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THE SECRETION OF URINE BY DEHYDRATED AND NORMAL INFANTS

BY

W. F. YOUNG, M.B., D.C.H., AND R. A. McCANCE, M.D., F.R.C.P.

WITH SOME TECHNICAL ASSISTANCE FROM E. FINCH, M.Sc.

(From the Children's Hospital, Birmingham, and the Department of Medicine, Cambridge)

The subject of gastroenteritis and its attendant dehydration and salt deficiency has absorbed the interest and attention of all those who have been responsible for the care of infants. The serum chemistry of babies with diarrhoea and vomiting has been carefully investigated, and a few authors have examined the urine and carried out renal function tests.

High blood ureas have been found in untreated cases (Schloss, 1918; Bessau, Rosenbaum and Leichtentritt, 1922; Cohen, Miller and Kramer, 1933), and Schloss considered that haemoconcentration was not enough to account for this finding. By means of the phenolsulphonphthalein test and Ambard's coefficient of urea excretion he showed that the function of the kidney was impaired in a group of infants recovering from gastroenteritis. Schoenthal, Lurie and Kelly (1933) came to the same conclusion after examining the urea clearances of a few babies who were dehydrated. The controls in both these investigations were normal infants whose urine volumes were usually much higher than those of the sick infants.

A number of observations on the changes in the serum electrolytes have been recorded. It has been found that the bicarbonate may be diminished or increased and that the chlorides may be low or extremely high (Aldridge, (1941a). Both chlorides and bicarbonate may be high in the same patient, which suggests that the excretion of sodium may have failed.

Darrow and Buckman (1928) found that an increase in the concentration of organic crystalloids of the plasma might be associated with a diminished plasma volume, and suggested that the excretion of minerals might be deficient when the urine was scanty. Hamilton, Kajdi and Meeker (1929) recorded instances of a type of acidosis in which the total base in the plasma was high and the percentage bound as chloride was raised. They considered that functional renal deficiency and haemoconcentration might explain these changes.

Cooper (1937) found that chlorides were increased in the tissues of infants who had died after saline had been administered, and considered that this was due to renal insufficiency. Hartmann (1928) noted that chlorides were raised, and bicarbonate correspondingly reduced, in the plasma of infants whose losses by diarrhoea and vomiting were such that the volume of saline

administered did not relieve their oliguria. Hoag and Marples (1931), however, considered that, except in moribund infants, the oliguria could always be overcome if enough fluid, including large volumes of parenteral saline, was given, and with this Cohen et al. (1933) agreed. The latter found in addition that this treatment restored the blood urea to normal. Nevertheless, these authors admitted that there was a risk of oedema in such treatment, and that the readjustment of the normal inorganic equilibrium of the blood might take some days. Day-to-day observations by Aldridge (1941b) have shown that the chlorides in the plasma may reach very high levels following the administration of saline in conventional amounts. Maizels and McArthur (1928–29) made a study, not only of the constituents of the blood, but also of the urine. Their observations were in some respects incomplete, but they recorded findings which seemed to implicate the kidney. They showed, for example, that raised plasma chlorides did not necessarily lead to a high concentration of chlorides in the urine, even if this fluid contained a high percentage of urea. Unfortunately, they did not measure the blood ureas of these cases or the minute volumes of the urine. These authors also noted that some of their patients were passing an acid urine when the pH of the plasma was high. Hartmann and Smyth (1926) had previously shown that the kidney might produce an acid urine from a plasma in which the bicarbonate was raised if the total base, i.e. the osmotic pressure of the plasma, was at the same time reduced. Maizels and McArthur (1929–30), however, found that the concentration of bicarbonate and chloride in the plasma were sometimes both raised and that therefore the osmotic pressure of the plasma must then have been above the normal level. They considered that an altered renal threshold for base consequent upon renal damage accounted for these observations.

It has never been suggested that infants with diarrhoea and vomiting suffer from ' nephritis.' It seemed possible, however, that they might have some functional disorganization of the kidney analogous to that studied by Borst (1938) and Black and Leese (1940) in haematemesis, McCance and Widdowson (1937a, 1937b and 1939) in alkalosis, experimental salt deficiency and diabetic coma, and by Allott (1939) in lesions of the central nervous system. It seemed desirable, therefore, to make a study of the kidney function of infants with diarrhoea and vomiting, and for this purpose to adopt the methods introduced by Möller, McIntosh and Van Slyke (1929) and Smith (1937), and used by McCance and Widdowson (1937, 1939) in their studies of functional renal disorganization. Since McCance and Young (1941) had recently shown that the kidneys of newborn infants functioned differently from those of adults, it was necessary to choose normal infants of the same ages as controls.

Present investigation

Subjects and methods. The subjects of the investigation included forty-one infants admitted to the gastroenteritis ward of the Children's Hospital, Birmingham, and twenty normal male babies who were convalescent. Strictly speaking, no hospital inmates can be regarded as normal, but when these babies were tested they were apyrexial and gaining weight, although some were still below the standard weight for their age. A few had been suffering from gastroenteritis and had, therefore, been examined previously.

The kidney function of infants with gastroenteritis and that of their normal

fellows has been compared. Since a previous investigation (McCance and Young, 1941) had shown that the clearances of urea and electrolytes per metre of surface area were low at birth, and increased to the adult levels during the first year of life, the patients and the controls have been divided into two age groups: (1) those aged five to twelve weeks; (2) those aged three to eight months. Surface area has been used as the basis when the function of one age group was being compared with that of the other or with that of adults.

The male infants were nursed in cots with the head end raised about six inches. The buttocks were placed on a rubber ring and the trunk supported on pillows. Restrainers were put on the more active subjects. The urine was collected in pyrex boiling tubes, which with a little practice could be so adjusted with strips of elastic strapping that the child was not inconvenienced and no urine was lost. The infants were allowed to void urine spontaneously, and each specimen was accurately timed and removed as soon as it was passed. The first was discarded, and subsequently each was analysed separately.

Blood was obtained from the heel or through the fontanelle; the latter was used only if inulin had been given. Inulin was administered if intravenous therapy was being undertaken, and in these circumstances 4 to 8 gm. were given by vein before the kidney function tests were to be made. Samples of blood were withdrawn at suitable intervals as the concentration of inulin in the plasma fell. A curve for the plasma inulin was then drawn covering the experimental periods, and inulin clearances were thus calculated for two or three specimens of urine. In calculating clearances, plasma values at the mid-point of each period were read off the curve. The urines for these tests were diluted while still warm to maintain the inulin in solution.

When inulin clearances were not being carried out, blood for the tests was taken so far as possible midway through periods of urine collection. In all samples of blood, except those used for urea alone, the corpuscles were separated as soon as possible and discarded. Serum was used for the estimation of potassium, but heparinized plasma for all the other analyses. When chlorides or bicarbonates were to be determined, the blood was taken and the plasma separated from the corpuscles under paraffin.

The chemical estimations were made in the way described by McCance and Young (1941) and Young, Hallum and McCance (1941).

The blood pressure was taken at intervals during the observations on dehydrated babies, and several times during each inulin experiment. It was intended to use the range of sphygmomanometer cuffs recommended by Robinow, Hamilton, Woodbury and Volpitto (1939), but at first these were not all available. The same sized cuff, however, was always used for the same child and it is believed that the blood pressures were within normal limits. Only one child's blood pressure rose appreciably with the relief of dehydration, and no significant changes of blood pressure took place during any of the inulin experiments, or when urea and other clearances were being determined. It is usual for children with diarrhoea and vomiting to collapse and become almost pulseless with low blood pressures as death approaches. They may collapse in this way for short periods and recover their previous blood pressures. Both these forms of collapse have been observed and recorded, but they have not happened at times which interfered with the studies of kidney function.

Results. SERUM CHEMISTRY. Reference has already been made to some of the changes in the serum chemistry of infants with gastroenteritis. All the abnormalities recorded by previous workers have been observed, and the circumstances under which they have been noted will be discussed when the results of the kidney function tests are being described.

URINE VOLUME. Brock, Thomas and Peiper (1934), Cohen et al. (1933) and Aldridge (1941b) showed that oliguria was associated with the dehydration which follows diarrhoea and vomiting in infants by measuring the twenty-four hourly urine output of their patients. The present observations on the minute volumes of the urine have confirmed their findings. The inset diagrams in fig. 1 show a comparison between the frequency distribution of the minute volumes of infants aged three to eight months with and without gastroenteritis. It will be noted that thirty-one specimens of urine from infants with diarrhoea

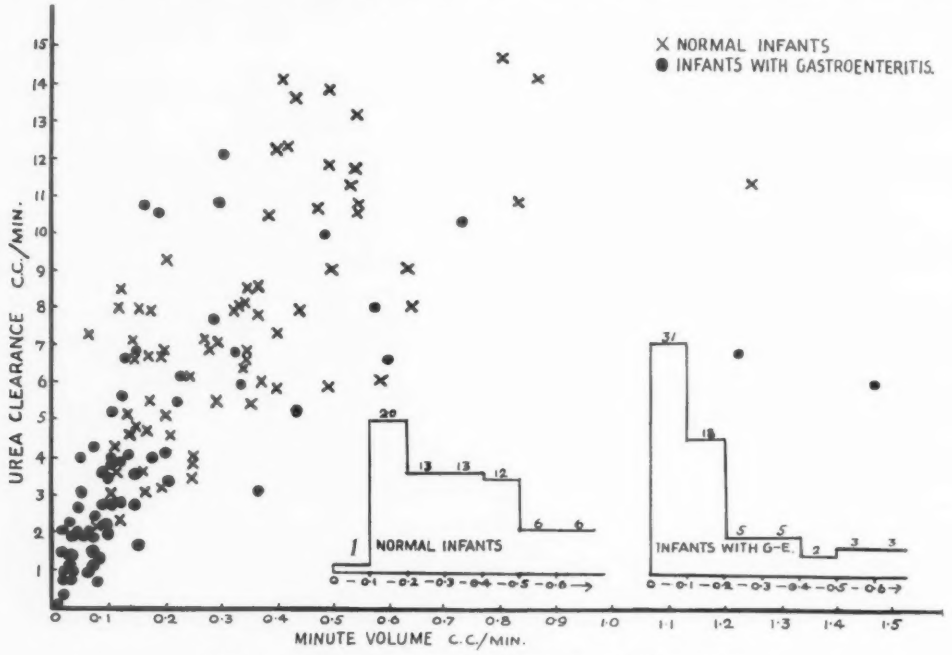

FIG. 1.—Urea clearances of infants aged 3–8 months.

and vomiting had a minute volume of less than 0·1 c.c./minute, whereas the minute volume of only one specimen from the normal infants was in this range.

When the infants with gastroenteritis were being studied, the periods during which the output of urine was measured included some when the dehydration of the patients had been relieved, even if only for an hour or two. Consequently the minute volumes of these samples were within the normal range. Since very low urine outputs were occasionally observed in some normal infants for short periods, the minute volumes of the two groups overlapped to some extent, and the comparison of their kidney functions was thus facilitated.

UREA CLEARANCES. Fig. 1 shows the urea clearances, $\frac{U V}{P}$, of all the older babies plotted against their minute volumes. The former ranged from 0·045 to 14·8 c.c./minute and the latter from 0·0072 to 1·47 c.c./minute. It will be noted that:

1. The clearances varied with the minute volumes.

2. The urea clearances of the infants with gastroenteritis were frequently very low when the minute volumes were low, but when the minute volumes

were in the normal range the clearances were comparable with those of normal babies. Moreover, on the few occasions when the minute volumes of the normal infants were low their urea clearances were correspondingly reduced.

It is probable, therefore, that the main reason for high blood ureas in dehydrated infants is their low output of urea, and that this in turn is due to their diminished flow of urine. This is supported by the fact that the blood urea may fall rapidly when the oliguria has been relieved. The blood urea of one of our patients fell from 186 mgm./100 c.c. to 55 mgm./100 c.c. in less than twenty-four hours.

Anything which reduces the volume of the urine tends also to produce low urea clearances. In the course of treatment some infants have become oedematous following the administration of too much salt. Some of the lowest minute volumes and urea clearances shown in fig. 1 were noted in infants who had been treated in this way. Low minute volumes and low urea clearances have also been described in premature infants who were oedematous (Young, Hallum and McCance, 1941).

Fig. 1 shows that at any one minute volume the urea clearances of the whole group varied over an extensive range. A variation from one child to another was to be expected, but the urea clearances of healthy individual infants were sometimes found to vary surprisingly from time to time. Some evidence was also obtained that as death approached, or if a child were in extremis, the urea clearances might fall below their 'normal' levels. Table 1 illustrates both these points.

TABLE 1

THE VARIATIONS IN THE UREA CLEARANCES OF INDIVIDUAL INFANTS

TIME	MINUTE VOLUME (C.C./MIN.)	UREA CLEARANCE (C.C./MIN.)
CASE 1. NORMAL INFANT AGED 15 WEEKS		
12.45 p.m.		
	0·17	6·72
–3.50 p.m.		
	0·18	7·98
–5.50 p.m.		
	0·20	3·25
–7.0 p.m.		
	0·25	3·84
–8.0 p.m.		
CASE 2. INFANT WITH GASTROENTERITIS AGED 6 WEEKS		
2.45 a.m.		
	0·097	2·32
–5.0 a.m.		
	0·222	3·75
–5.45 a.m.		
	0·086	2·50
–6.50 a.m.		
	lost	
–9·0 a.m.		
	0·069	0·36
–1.55 p.m.		
	0·078	0·65
–6.0 p.m.		
9·25 a.m.	Death	

Case 1 was a thriving child aged fifteen weeks; and on July 16 his minute volumes hardly changed from 12.45 to 8.0 p.m. Nevertheless, his clearances before 5.50 p.m. were approximately double those from 5.50 to 8.0 p.m. Case 2 was a marasmic infant, aged six weeks, suffering from gastroenteritis. There was a big fall in his urea clearances fifteen to twenty-four hours before death, although the minute volumes of his urine were comparable with those obtained earlier on the same day.

Fig. 2 shows all the urea clearances of the two age groups, averaged and corrected for surface area as described by Young, Hallum and McCance (1941), and compared with those of premature and full-term new-born infants and with those of adults. It will be noted that the clearances increased with the age of the subjects. It is evident from the averaged clearances of the older

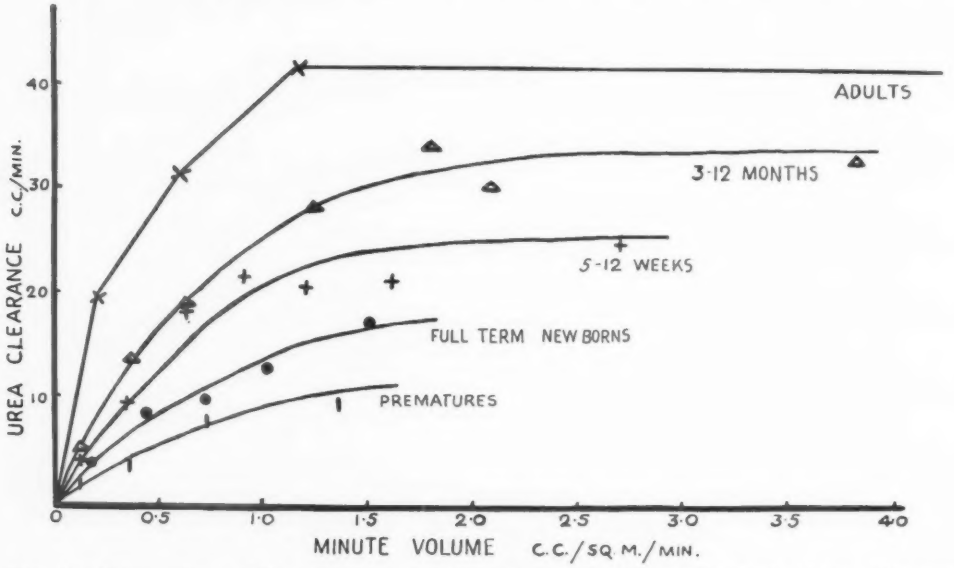

FIG. 2.—Comparison of the average urea clearances of adults and of infants at four different ages.

babies that some of the individual figures must have been very near the adult levels at high minute volumes. In each group of infants, however, the clearances varied more extensively with the minute volumes than they do in adults, so that, even among the older babies, clearances seldom approximated to the

TABLE 2

THE EFFECT OF URINE FLOW UPON THE $\frac{\text{INFANTILE}}{\text{ADULT}}$ UREA CLEARANCE RATIO

VOLUME OF URINE C.C./SQ.M./MIN.	AVERAGE INFANT UREA CLEARANCE C.C./SQ.M./MIN. / ADULT UREA CLEARANCE C.C./SQ.M./MIN.			
	PREMATURE / ADULT	FULL-TERM / ADULT	5–12 WEEKS / ADULT	3–8 MONTHS / ADULT
0·3	0·18	0·24	0·38	0·53
0·75	0·23	0·34	0·49	0·62
1·2	0·25	0·38	0·51	0·69

adult levels at low minute volumes. This is demonstrated by the ratios of infant to adult clearances which are shown in table 2. In no group of infants did the ratio reach 1·0, and it was always smaller at low minute volumes than it was at high ones.

The relationship between the urea clearances and the glomerular filtration rates

The glomerular filtration rates (measured by the inulin clearances) of a few infants with gastroenteritis were estimated at the same time as the urea clearances. The results are shown in table 3. It will be noted that :

Table 3

Inulin and urea clearances

Name	Urine volume c.c./sq.m./min.	Inulin clearance c.c./sq.m./min.	Urea clearance c.c./sq.m./min.	$\frac{U}{I}$ clearance ratio
T	0·430	12·5	6·5	0·52
	0·485	11·6	6·9	0·59
	1·150	18·6	11·6	0·62
R.	0·087	9·5	3·0	0·31
	0·174	16·1	6·1	0·38
B.	0·361	39·8	11·3	0·28
	0·364	43·0	13·3	0·31
	0·266	44·4	15·6	0·35
C.	0·502	30·2	9·5	0·31
	2·080	50·1	23·4	0·46
	4·350	51·2	24·2	0·47
	5·180	45·0	21·2	0·47
A.	0·192	14·7	3·1	0·19
	0·221	17·3	4·7	0·22
	0·302	19·5	6·4	0·30
Ta.	0·442	14·8	10·4	0·70
	1·060	22·8	19·1	0·83
Sm.	0·630	26·9	15·7	0·56
	2·080	61·8	29·5	0·48

1. The inulin clearances are all lower than the adult standard which may be taken to be 70 c.c./sq.m./min. These observations, which were made in 1939, are in agreement with the findings of Barnett (1940), who employed an indirect method to estimate the inulin clearances of some newborn infants and others aged two to seven-and-a-half weeks. He found that on the basis of surface area the inulin clearances at birth were less than 50 per cent. of those in adult life. As he did not collect the urine of his subjects the minute volumes at the times at which the clearances were measured are unknown.

2. A change of any magnitude in the minute volumes was always accompanied by a change of the clearances in the same direction, but it is clear from baby C that there is probably a limit above which a further increase in the minute volume leaves the clearances unchanged.

3. The $\frac{U}{I}$ clearance ratios were of the same order as those previously found in adults and newborn babies.

4. The $\frac{U}{I}$ clearance ratios tended as in adults to increase with the minute volume, but this effect was small compared with the changes induced in both inulin and urea clearances by changes in the minute volumes. It would seem, therefore, that the urea clearances of infants may be used as a guide to the behaviour of the glomerular filtration rates, and, if a sufficient number of inulin clearances had been carried out, a progressive increase with age would almost certainly have been found (fig. 2). It has been stated that the glomerular filtration rate of adults and of dogs remains relatively constant over the normal range of minute volumes (Smith, 1937), and only falls when the minute volumes are very small (Chesley, 1938; Steinitz and Türkand, 1940), or in functional renal disorganization due to disease (McCance and Widdowson, 1939; Black, Powell and Smith, 1941). The evidence which is now presented suggests that during infancy the glomerular filtration rate is lower and not nearly so stable as it is in adult life. If this be true, then the excretion of minerals and of waste products of metabolism other than urea must also be affected by these characteristics of the glomerular filtration rate.

Two recent studies of the histology of the kidney in infancy add interest to the present findings. Gruenwald and Popper (1940) examined the renal glomerulus in early post-natal life, and observed that until birth the glomerular loops were matted together and invaginated in a sac of high columnar epithelium. After birth the epithelial sac burst and the loops expanded, but in early postnatal life the peaks of the loops were still covered with high columnar epithelium. Gruenwald and Popper considered that this layer might impede glomerular filtration. The low glomerular filtration rates which have been described suggest that it does. Kaufmann (1940) studied the juxta-glomerular corpuscles of Goormaghtigh in normal and diseased human kidneys removed surgically and at autopsy. These special groups of cells are situated chiefly at the vascular pole of the glomerulus and may be concerned with the regulation of the glomerular filtration rate. They were not observed in the kidneys of stillborn infants or children up to the age of two years. It is thought that their absence may explain the instability of the glomerular filtration rate in young children.

THE EXCRETION OF MINERALS. The excretion of electrolytes is governed by factors other than the glomerular filtration rates and the minute volumes. The ions in question all belong to the so-called threshold class of substances, and a small rise or fall in their plasma concentrations may make an enormous difference to their output in the urine. To some extent, moreover, the suprarenal cortex governs the reabsorption of sodium, chloride and potassium in all animals, and in dogs the posterior pituitary has also been shown to be concerned with the concentration of chlorides in the urine (Paine and Nelson, 1939). Leiter (1941) indeed took the view that 'extrarenal factors are too important in the case of the major electrolytes to justify the expectation of much progress from . . . clearance studies.' This seems to have been unwarrantable

pessimism, for a study of clearances alone has been enough to show that there are certain interesting differences between infants and adults in the way in which electrolytes are excreted. Thus the sodium, chloride and potassium clearances of premature and full-term normal infants have already been shown to be of a very low order compared with those of adults on the basis of their respective surface areas. As might have been expected, the clearances of normal babies aged two to six months have now been found to lie between those of newborn babies and of adults. This finding, however, will not be further discussed since this study has been concerned primarily with infants suffering from the effects of dehydration.

THE CHLORIDE AND SODIUM CLEARANCES. The concentration of chlorides in the plasma of untreated patients with gastroenteritis is often above normal limits (Aldridge, 1941, a, b), and it may reach very high levels after the administration of saline. The reluctance, by adult standards, of the infant kidney to excrete chlorides can easily be demonstrated by the following consideration. The average concentration of chloride found in the urine of infants, whose plasma chlorides were above 400 mgm./100 c.c., was 314 mgm./100 c.c. In adults a figure round 1 per cent. would have been expected if forced excretion of chlorides was in progress (Baird and Haldane, 1922; de Wesselow, 1925–26).

Fig. 3 shows the chloride clearances of all the infants aged three to eight

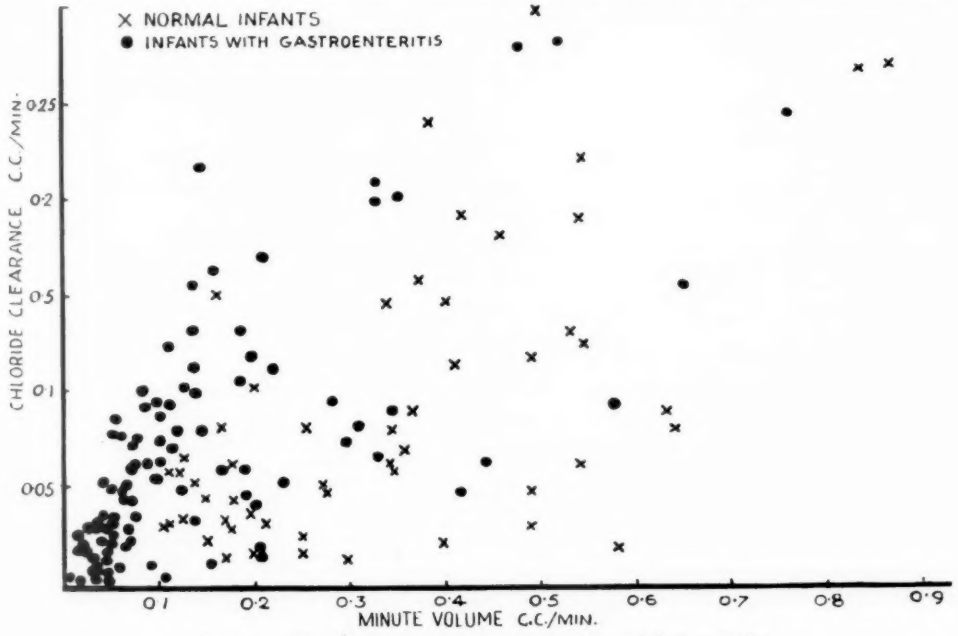

FIG. 3.—Chloride clearances of infants aged 3–8 months.
(For graphical convenience seven chloride clearances above 0·3 c.c./min. and three at minute volumes over 0·9 c.c./min. have been omitted.)

months, whether they were normal or suffering from the immediate or subsequent effects of dehydration. The scatter is very great, and further analyses of these results will be made, but fig. 3 shows quite clearly that, although there is a tendency for the clearances to vary with the minute volumes, at com-

parable minute volumes the clearances of the children suffering from diarrhoea and vomiting were fully as high, and often much higher, than those of normal children of the same age. This certainly does not suggest renal failure, but it must be recalled that the concentration of chloride in these sick babies' plasma was often above normal, and that this might in itself be expected to raise the clearances, and might out-weigh other factors which were depressing them. Accordingly, the plasma chlorides and the clearances have been averaged at comparable minute volumes and the results are given in table 4. It will be seen that, as suggested by fig. 3, at all comparable minute volumes the clearances of the sick children were higher than those of the normal. At most minute volumes, however, the plasma chlorides were also higher, so that the clearances are not directly comparable. At urine volumes between 0·2 and 0·3 c.c./minute, however, the plasma chlorides were the same, and the clearances of the sick children higher. This evidence, therefore, indicates that their kidneys were functioning quite normally, by infant standards, and in this it corroborates the conclusions reached from a study of the urea clearances. Table 4 also shows that the clearances of the sick children varied with the minute volumes much more extensively than did the clearances of the normal children. The minute volume is obviously a factor limiting the clearances of babies who are, or who have been, dehydrated and whose plasma chlorides are raised. The minute volume, indeed, seems much more important under these conditions than the actual plasma level. This is clearly brought out by a study of table 5, which shows the sodium and chloride clearances at various minute volumes of all the sick children whose plasma chlorides exceeded 400 mgm./100 c.c., i.e. were grossly raised. It will be noted that the smaller the minute volumes

TABLE 4

A COMPARISON OF THE AVERAGED CHLORIDE CLEARANCES OF INFANTS WITH AND WITHOUT GASTROENTERITIS

	MINUTE VOLUME C.C./MIN.	NORMAL INFANTS		INFANTS WITH GASTROENTERITIS	
		PLASMA CHLORIDE MG./100 C.C.	CHLORIDE CLEARANCE C.C./MIN.	PLASMA CHLORIDE MG./100 C.C.	CHLORIDE CLEARANCE C.C./MIN.
Infants aged 3–8 months :	0·0–0·1	385	—	417	0·037
	0·1–0·2	351	0·064	394	0·091
	0·2–0·3	366	0·042	366	0·074
	0·3–0·4	366	0·145	411	0·266
	0·4–1·0	363	0·130	388	0·316
	Over 1·0	381	0·122	416	1·220
Infants aged 5–12 weeks :	0·0–0·1	348	0·012	424	0·024
	0·1–0·2	382	0·021	382	0·049
	0·2–0·3	378	0·051	398	0·129
	0·3–0·4	383	0·071	—	—
	0·4–	372	0·054	—	—

the lower were the chloride clearances, although, at the same time, the higher were the plasma chlorides. The same relationships hold for the sodium clearances and the plasma sodiums of the older babies (also shown in table 5). The sodium figures for the younger babies are the means of only four and five individual assays. They have, therefore, less significance than the others, and while they show like them an increase of the clearances with the minute volumes they indicate that the rise in the plasma sodiums may have had something to do with this result.

TABLE 5

THE EFFECT OF URINE FLOW UPON THE AVERAGED CHLORIDE AND SODIUM CLEARANCES OF INFANTS WHOSE PLASMA CHLORIDES WERE OVER 400 MGM./100 C.C.

	MINUTE VOLUME	PLASMA CHLORIDE (MGM./100 C.C.)	CHLORIDE CLEARANCES (C.C./MIN.)	PLASMA SODIUM (MGM./100 C.C.)	SODIUM CLEARANCES (C.C./MIN.)
Infants aged 3–8 months :	0·054	464	0·040	345	0·016
	0·142	452	0·099	339	0·036
	0·295	430	0·246	317	0·164
	0·771	420	0·730	298	0·232
Infants aged 5–12 weeks :	0·032	444	0·011	338	0·020
	0·079	412	0·044	376	0·023
	0·3 *	418	0·213	—	—

* One sample only.

The fact that there has been a closer relationship between the minute volumes and the chloride clearances in the sick infants than there has been in the normal ones can be explained as follows, and is in keeping with some of the observations which have been made upon chloride excretion in adults. When the plasma chlorides are at or near the ' threshold ' value, or when for some hormonal reason (Thorn, Engel and Lewis, 1941) the excretion of chlorides is more or less in abeyance, the urine formed at the same time, whatever its volume, can easily carry the quota of chlorides assigned to it without straining the energetics of the renal parenchyma. When, however, the plasma chlorides are high, or a high rate of excretion is demanded, then the amount of chloride to reach the bladder is determined by urinary and renal limitations such as the osmotic pressure of the urine, and its volume. An association between minute volume and chloride output, similar to the one now being presented in dehydrated or over-treated infants, was found by de Wesselow (1925–26) in adults who had taken 4 gm. of sodium or potassium chloride. Three hours later the chlorides in the urine had always risen to about 1 per cent. although the volumes varied from 50 to 132 c.c./hour at the same time. Baird and Haldane (1922) studied the adult response to much larger doses (38 gm.) of sodium chloride, taken by mouth as hypertonic or isotonic solutions. They showed that the concentration of chloride in the urine rapidly rose to a steady value of about 1·03 per cent. whatever the diuresis, and remained there for some seven or

eight hours. Had the chloride clearances been determined either by de Wesselow or Baird and Haldane they would have been found to vary closely with the minute volumes.

The sodium in the plasma is frequently low (not high) in untreated cases of gastroenteritis, and this may be one of the factors limiting the excretion of chlorides in such children. During treatment with saline, however, the serum sodiums may rise to very high levels, and in four babies, figures above 380 mgm./100 c.c. were recorded. Even at these plasma levels, however, the clearances were very low at low minute volumes.

POTASSIUM CLEARANCES. Hall and Langley (1940) have studied the excretion of potassium by three normal adults. They found that, when the intakes in the food were approximately constant, the plasma potassium of their subjects remained at about 17 mgm./100 c.c. and the clearances were maintained at about 16 c.c./sq.m./min. at all minute volumes above 0·6 c.c./sq.m./min. When the minute volumes fell below this level, however, the clearances fell too, and a reduced glomerular filtration rate was put forward as the explanation. If this is correct, and if the evidence already presented be accepted that in infancy the glomerular filtration rates vary with the minute volumes over a much wider range than they do in adults, then one would expect to find that, in infancy, the potassium clearances varied with the urine flow, and particularly with the urea clearances, over the whole range of minute volumes. The potassium clearances of each child were, therefore, compared with his urea clearances arranged in ascending order. The clearances of a few cases which were selected more or less at random are shown in table 6, and they demonstrate that the expectation that the potassium clearances would vary with the urea clearances was correct. Few exceptions were found among the normal infants, and generally speaking the same was true of the infants who were suffering from dehydration, but among them it was noticed that the first specimen passed as the dehydration was being relieved gave an exceptionally high potassium clearance. There is no obvious explanation for this at present, but it seems wise to put it on record. It has already been shown that dehydration does not as a rule reduce the urea clearances except in so far as it reduces the minute volumes. This appears also to be true of potassium, for the $\frac{\text{urea clearance}}{\text{potassium clearance}}$ ratios (table 6) were not demonstrably higher in children who were suffering from the effects of dehydration. It may, however, be noted in passing that the clearance ratios of the infants with gastroenteritis varied very much more than those of normal infants. The range was 1·9 to 23·0 for the normal infants, and 0·46 to 80·6 for the infants suffering from gastroenteritis.

THE OSMOTIC PRESSURE OF THE URINE. In the previous investigations on premature and full-term infants, an indication of the relative osmotic pressures of the urine and of the plasma was obtained from the ratio

$$\frac{\text{m. eq. of urea} + \text{m. eq. of electrolytes in the urine}}{\text{m. eq. of urea} + \text{m. eq. of electrolytes in the plasma}}$$

TABLE 6

A COMPARISON OF THE UREA AND POTASSIUM CLEARANCES C.C./SQ.M./MIN.

INITIAL AND AGE OF SUBJECT	NORMAL INFANTS				INITIAL AND AGE OF SUBJECT	INFANTS WITH GASTROENTERITIS			
	UREA CLEARANCE C.C./SQ. M./MIN.	PLASMA POTASSIUM MGM./100 C.C.	POTASSIUM CLEARANCE C.C./SQ. M./MIN.	UREA CLEARANCE, POTASSIUM CLEARANCE RATIO		UREA CLEARANCE C.C./SQ. M./MIN.	PLASMA POTASSIUM MGM./100 C.C.	POTASSIUM CLEARANCE C.C./SQ. M./MIN.	UREA CLEARANCE, POTASSIUM CLEARANCE RATIO
F.	6·4	29·6	0·9	7·2	H.	11·1	23·0	13·0 *	0·9
(6½ weeks)	13·2	29·6	2·5	5·3	(7 weeks)	14·0	23·0	10·8	1·3
	24·1	29·6	5·0	4·8		18·4	23·0	10·8	1·7
T.	23·5	19·0	5·6	4·2	C.	9·5	24·0	3·1	3·0
(4½ months)	26·7	19·0	5·5	4·8	(4½ months)	21·0	24·0	10·9 *	1·9
	27·8	19·0	8·8	3·2		23·5	25·0	6·2	3·8
	37·6	19·0	10·3	3·7		24·1	26·0	9·2	2·6
G.					P.	5·9	26·5	13·0 *	0·5
(4 months)	12·1	18·0	1·4	8·4	(4 months)	7·7	26·5	5·2	1·5
	14·2	18·0	2·0	7·3			12-hr. interval		
	24·9	18·0	3·2	7·8		11·6	27·6	0·6	18·7
	29·5	18·0	3·1	9·5		15·9	27·6	1·3	12·3
	12·4	26·0	2·4	5·1	A.	3·1	20·0	0·6 *	4·8
H.	13·9	26·0	1·3	10·8	(4 months)	4·7	20·5	0·2	29·0
(5 months)	22·8	26·0	6·0	3·8		6·4	19·0	0·4	17·0
	12·3	26·8	2·2	5·7	T.	6·8	20·0	0·5	13·7
P.	16·1	26·8	3·3	4·8	(5½ months)	8·1	20·0	0·9 *	9·4
(4 months)	17·8	26·8	3·2	5·6		11·6	16·0	1·0	12·0
	19·3	26·5	2·6	7·3		20·2	17·0	1·5	14·0
	20·3	26·5	5·8	3·5		20·5	18·0	2·5	8·2
	20·7	26·5	6·3	3·3		32·7	19·0	2·6	12·4
	21·7	26·5	6·9	3·2			3-day interval		
	28·4	26·8	2·9	9·7		15·5	15·0	0·3	46·0
	32·0	26·8	7·7	4·2		28·4	15·0	3·9 *	7·4
	46·4	26·8	13·0	3·6		42·8	15·0	1·4	31·5

* First period of observation.

and it was found that this U/P ratio was very small by adult standards at comparable low and average minute volumes. Such small ratios are really another expression of the fact that, while the plasma concentrations of urea and electrolytes in healthy infants are similar to those of adults, their urines are much more dilute at low urine volumes, and consequently their clearances are considerably lower.

The U/P ratios of the groups of babies which have now been studied have also tended to be low. Fig. 4 shows the ratios of all the younger infants plotted

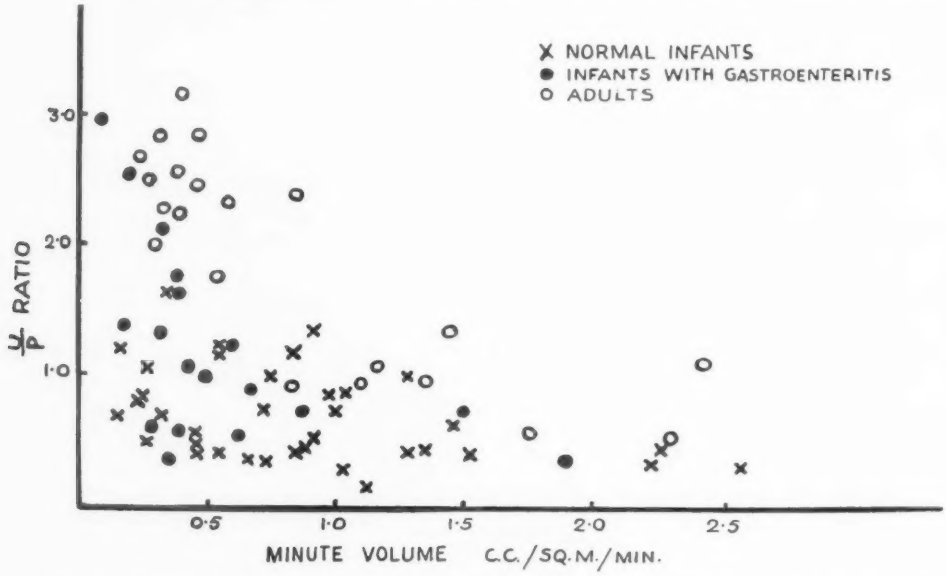

FIG. 4.—Comparison of the $\frac{\text{Urine}}{\text{Plasma}}$ crystalloid concentrations of infants aged 5–12 weeks and of adults.

against the minute volumes/sq.m./min., and the ratios of a few normal adults have been added for comparison. It will be noted that when the minute volume was below 0·5 all the adult ratios were above 2, whereas none of the normal infant's ratios reached this level. It will also be noted that there was no obvious tendency for the ratios of the sick children to be any lower than those of the normal children. In fact, the three highest baby ratios, all of which exceeded 2, were given by abnormal children, and further analysis of the data shows that they were all given by a single child whose blood urea was 136 mgm./100 c.c. The concentrations of urea in the three samples of this infant's urine were 3·02, 4·18 and 3·76 per cent. The effect of a high blood urea on the U/P ratio was discussed in connection with the premature infants. It was pointed out that the proportion of the osmotic pressure of the urine due to urea is usually a large one, but the greater part of the osmotic pressure of the plasma is due to electrolytes. Urea is not an important part even when the plasma ureas are high. Since the urea clearances in infancy usually seem to be unaffected by the height of the blood urea, even if this has been raised by dehydration and oliguria, the U/P ratios tend to increase rapidly as the blood urea

rises. This preponderating importance of urea in regulating the U/P ratios was clearly demonstrated in the investigation of premature infants, for in them the electrolyte clearances were usually so low that the concentration of minerals in the urine could almost (save in one exceptional infant) have been neglected. A high blood urea seems even at two or three months of age still to be the most frequent and most potent cause of a high U/P ratio, but factors which tend to raise the mineral output in the urine have to be considered more often at these ages. These have already been discussed in connexion with the excretion of electrolytes and seem to be: (1) an increased output of sodium chloride after saline administration. This was the cause of one exceptionally high ratio previously reported in newborn infants; (2) the high potassium clearances which have been found to follow the relief of dehydration.

These results corroborate the findings of Maizels and McArthur (1928–29; 1929–30) and show how their limited data led them to what now appears to have been an erroneous conclusion. These authors interpreted their results as indicating specific failure of the kidney to excrete minerals. They were probably dealing with the normal response of infants to dehydration. They might have modified their suggestions had they had the opportunity to investigate normal infants.

Discussion

The results of this investigation invite discussion under two headings. The first is the kidney function of the normal control series and its relationship to the same function in adults and in younger children. In general terms this is not difficult, although there are still many details which are obscure. It may be stated broadly that infants of the ages here investigated have kidneys which are functionally intermediate between the adult and newborn types. Their urea clearances show their transitional position very well (fig. 2) and their inulin and mineral clearances fall into the same place. It is evident, therefore, that the adult type of function is not acquired in the first few weeks or even months of life, and probably not till at least the end of the first year. Traces of the infantile type of function may even persist in some children till well into the second year, and indeed the excretion of minerals has been so little investigated at all ages, that interesting developmental changes may be met with until much later in life.

The ways in which infants' kidneys differ functionally from adults may now provisionally be summarized, all comparisons being made on the basis of surface area. They have much lower glomerular filtration rates and urea clearances, and both vary much more extensively with the urine volumes than they do in adults—at any rate at normal flows. There is a lack of information, however, about the adult glomerular filtration rate at some urine flows which makes it difficult to be more explicit on this matter. Infants have much lower mineral clearances than adults, and even when there is positive evidence from plasma levels, or the quantities of saline administered, that the organism must be overloaded with salt, the concentration of chlorides in the urine is often very low. When the output of urine falls, the infant does not increase the

concentration of solutes in his urine in the way an adult does, and consequently, with minor exceptions which have been discussed, an infant's urine is always (even at low minute volumes) a dilute urine. Kerpel-Fronius (1931) studied the response of a dog, ten days old, to a ' dehydration ' diet, and compared it with that of a dog aged four months. He showed that the maximum concentration of nitrogen in the urine of the young dog was much lower than in that of the older dog. The observation suggests that man is not the only mammal in which the adult type of kidney function has not been established at birth.

The results here set out help to explain many well-known features of child health and disease. They show, particularly, why infants tolerate dehydration so badly, and misguided treatment almost worse. It is clear now why two or three large vomits and several watery stools may send a baby's blood urea up to 100 mgm./100 c.c. in a single day, and why the enthusiastic administration of a pint of normal saline may lead to unmistakable oedema. It is even conceivable that renal failure and nitrogen retention may precipitate diarrhoea and vomiting as a complication in babies who are suffering from some other disease. Schoenthal's (1929) work on one baby suggests that this may be so, and uraemic vomiting and diarrhoea are common enough in adults.

The second point for discussion is the effect of dehydration—caused by diarrhoea and perhaps vomiting as well—on the kidney. As outlined in the introduction, many have thought that diarrhoea and vomiting with their attendant dehydration brought about positive renal deterioration. This may to some extent be true, but the results which have now been obtained indicate that these suggestions were made by persons with insufficient knowledge of the function of the normal infant's kidney. The evidence here presented all goes to show that, whereas dehydration rapidly alters the serum chemistry in ways which suggest functional disorganization of the kidney, this organ is usually functioning in a perfectly normal infantile manner. As Schloss suggested as long ago as 1918, the pathological changes in the serum chemistry are due largely, and often solely, to the small quantity of water available for excretion.

Summary

1. Infants aged one to eight months have been found to have kidneys which are intermediate in functional capacity between those of adults and those of newborn children.

2. They have lower glomerular filtration rates and urea clearances than adults, expressed on the basis of surface area, and both vary with the minute volumes at normal rates of urine flow. The mineral clearances also tend to be lower than in later life. The solids in the urine do not rise as in adults when the minute volumes fall. Consequently, infants fail to maintain a constant internal milieu the moment they begin to pass small volumes of urine.

3. No evidence has been obtained that children who have been made short of water by diarrhoea or vomiting have a specific renal lesion. Their kidneys are functioning in the normal infantile manner and the abnormalities in their serum chemistry are due to the small amount of water available for excretion.

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PEPTIC ULCER IN INFANCY AND CHILDHOOD WITH A REVIEW OF THE LITERATURE

BY

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The occurrence of peptic ulcer in infancy was described over a hundred years ago by Cruveilhier (1829–35) in his ' Anatomie Pathologique du Corps Humain '. He records the presence of multiple gastric ulcers in three infants at the respective ages of one, two, and four weeks. The lesions are clearly illustrated by drawings. Since then reports on peptic ulcers in children have appeared in ever-increasing numbers in the literature (chiefly continental and American), Theile (1919a) having collected 248 cases under the age of sixteen, while Bird, Limper and Mayer (quoted Ladd and Gross, 1941) review 243 cases up to the age of fifteen. In this country, however, according to Paterson, only three British cases were published prior to 1922. In view of this dearth a series of such cases is here reported in order to draw attention to the condition, since the first essential for the diagnosis of peptic ulceration in childhood is recognition of the fact that it actually does occur, even in the neonatal period. Theile, who saw it from the first day of life onwards, considers that it almost always arises after birth, and this is confirmed by Ballantyne (1902) in his ' Textbook of Antenatal Pathology '. Some authors, however, believe that the lesion may be present at birth. According to Ladd and Gross it has been described in stillborn infants. It is well known that acute peptic ulcers can develop very quickly, having been seen as early as nineteen hours after a severe burn (Hurst and Stewart, 1929).

It is possible that in newborn infants with a very delicate gastro-intestinal wall ulceration may progress still more rapidly; hence an intrauterine origin for ulcers need not be assumed even in infants dying shortly after birth.

Clinical material

The cases to be described, nine in number, all came to autopsy in the Glasgow Royal Hospital for Sick Children, between the years 1914 and 1941, and are included in a series of 6059 post-mortems on children under the age of thirteen. Most of the subjects coming to necropsy in this institution are infants, approximately two-thirds of those examined during the last ten-year period having been under the age of one year.

Case 1 of the series is described below in some detail, as the clinical and pathological features are typical. The post-mortem examination was per-

formed by the writer and the interest it aroused prompted a search through the autopsy records of the hospital when the other eight were forthcoming. These are relegated to an appendix.

Case 1, H. L., female, aged ten weeks, born after a normal full-time pregnancy, was admitted on December 22, 1940. She had been well until December 17 when vomiting and green diarrhoea began. Breast milk had been given for one month, afterwards diluted cow's milk. On admission the child was well-nourished, but anaemic and collapsed. The abdomen was lax. No improvement resulted and on December 24 bright red blood was passed per rectum for the first time. Copious rectal haemorrhages recurred despite administration of vitamin K and blood transfusion. The child died on December 26. At autopsy an ulcer measuring 1·25 by 1·5 cm. was present on the posterior duodenal wall just beyond the pylorus. It was terraced at the deeper pyloric end. In the base was an eroded vessel, the source of the blood which filled the stomach and bowel. The ulcer was firmly adherent to the underlying pancreas and the tear seen in the specimen was probably produced on separating the adhesions. The thoracic and abdominal viscera, the peritoneal and other serous sacs were free from gross morbid change, and the brain was normal. Double otitis media was present. On histological examination it was found that the ulcer had eroded all coats of the bowel so that the base was formed by pancreas. No inflammatory reaction had occurred, the lesion being purely destructive. There was no sign of haemorrhage, old or recent. No organisms were seen in Gram-stained sections. Several large arterioles were present in the vicinity of the ulcer base.

Age and sex incidence of peptic ulcer in childhood

Four of the patients were male, five female. Sex distribution appears to be approximately equal in early life, as Theile also found. All our subjects were under the age of twelve months except a girl six years old in whom the ulcer was in all probability traumatic in origin and is therefore in a special category. The infantile cases will be considered together. Six of these were under the age of three months, the youngest having survived only for three days.

The occurrence of peptic ulceration in early infancy is amply confirmed by others. Holt (1913) states that of sixty-five patients with duodenal ulcer 70 per cent. died before the fifth month of life, nine actually within the neonatal period. Of Theile's series one-third succumbed in the first month of life. More recent single reports of neonatal deaths from peptic ulcer are also extant. Butka (1927), Nixon and Fraser (1928), Somerford (1930), Brockington and Lightwood (1932), Dunham and Shelton (1934), Craig (1934), Kunstadter and Gettelman (1936) all publish cases fatal in the first fortnight. Craig's case, a premature infant born six weeks before term, survived only thirty-four hours. Kunstadter and Gettelman's report concerns an infant, also premature, who succumbed on the fourth day of life. A successful operation on a thirty-four-and-a-half-hour-old baby with a perforated duodenal ulcer is recorded by Bird, Limper and Mayer (Ladd and Gross, 1941).

Etiology of ulceration

Circulatory disturbance. Peptic ulceration in neonatal life has been attributed to circulatory disturbance of the gastro-intestinal tract at the time of

birth especially in prolonged or difficult labour. Either asphyxia with consequent duodenal congestion and possibly mucosal haemorrhage, or ischaemia resulting reflexly from vascular spasm, may lead to devitalization of the mucous membrane with subsequent peptic digestion of the damaged area. Irritation of the vasomotor centres in the brain as a result of cerebral haemorrhage may also affect the duodenal circulation. Further, the mechanical factor of pressure comes into play at times, according to Aschoff (quoted by Pfaundler and Schlossmann, 1935), who describes anaemia of the duodenum resulting from compression of that structure between liver and head of pancreas during birth. With the post-partum influx of blood mucosal haemorrhage is liable to occur, followed by digestion of the blood-infiltrated area. The importance of a normal blood-supply in maintaining the integrity of the duodenal mucosa is confirmed by Theile who states that any serious disturbance of circulation may be the starting point of a duodenal ulcer.

That the gastric juice even in early infancy possesses considerable powers of peptic digestion is demonstrated by the work of Miller (1941) who found that its acidity is surprisingly high, reaching a maximum within forty-eight hours of birth when it is equivalent to that of a healthy adult; thereafter it falls rapidly and remains low during infancy. This high gastric acidity would appear per se to be an important factor in inducing peptic ulceration at an early age.

Trauma. Trauma as well as circulatory disturbance may damage the gastro-intestinal mucosa in the newborn. Instruments introduced for the purpose of clearing the trachea at birth may enter the stomach and abrade the mucosa as in the case reported by Kunstadter and Gettelman (1936). These authors also saw multiple gastric erosions associated with congenital duodenal stenosis, and they attribute mucosal injury to hyperperistalsis and vomiting induced by the attempt to empty the stomach. Burdick (1940) also describes a duodenal ulcer in a three-week-old mongol with a congenital obstruction at the duodeno-jejunal junction. In a case of the present series mucosal irritation and subsequent ulceration may fairly be attributed to excessive dosage with oleum ricini in the first two weeks of life. Gastric ulcers caused by swallowing caustic fluid are reported in two young children by Hurst and Stewart (1929). Of course, irritation of the gastro-intestinal mucosa may also result from unsuitable feeding in early as in later infancy.

Sepsis. Sepsis plays a part in the production of peptic ulcer both in the neonatal period and later; a type of sepsis peculiar to early infancy is umbilical infection, of which Dunham and Shelton (1934) describe an instance. Here, staphylococcal omphalitis was followed by septic thrombosis of the umbilical vein, with resulting septicaemia, leading finally to ulceration of the gastric mucosa. As with increasing age conditions approximate more closely to those in adults, sepsis comes to play a more prominent etiological rôle in peptic ulceration. Numerous reports demonstrate the association between diverse septic lesions and gastro-duodenal ulcers in infants and children. Hurst and Stewart state regarding the part played by bacteria in the production of ulcer, ' It is clear that the gastric lesion is caused by bacterial toxins. These may be produced locally by organisms situated in the small vessels of the gastric

mucous membrane to which they have been conveyed by the blood stream or they may be produced in the primary site of the disease from which they are carried by the blood to be excreted by the gastric mucous membrane.' Of five children under the age of three years in whom gastric ulcers were found by these authors, three died respectively of meningococcal meningitis, empyema and coeliac disease.

Theile (1919a), Brüning and Schwalbe (1913) and others found duodenal ulcers associated with suppurative appendicitis. Borland (1903) saw one in an infant with an acute exacerbation of eczema of the head and face. In the case reported by Harkins (1938) a duodenal ulcer was the sequel to a large scald which became septic. There is one type of sepsis, i.e. suppurative meningitis, which appears specially prone to induce peptic ulceration. Doubtless the nervous element plays a part here as well as the actual sepsis. Berglund (1929) saw meningitis in six out of twenty children with peptic ulceration. Webster (1938), Hartung and Warkany (1938) and Letondal (1940), all report duodenal ulcer in infants with purulent meningitis, either tuberculous or acute. Hurst and Stewart's case of gastric ulcer and associated meningococcal meningitis has been mentioned, and further examples of combined ulcer and meningitis occur in various textbooks of paediatrics. No like instance occurred in our series.

Peptic ulcers may also arise in the course of the various exanthemata and likewise in toxaemic conditions, e.g. uraemia. The etiological relationship between infection and ulcer is well illustrated in the case reported by Proctor (1925), that of a young child with a chronic duodenal ulcer, in whom repeated upper respiratory infections provoked acute exacerbations with melaena and haematemesis. John (1938) reports somewhat similar findings in the case of a boy aged six years with an indurated ulcer of duodenum.

Burns and scalds. At one time duodenal ulcer was considered a fairly frequent concomitant of burns and scalds. Thus Perry and Shaw (1893) found peptic ulcers in 3·3 per cent. of subjects suffering from burns, while the incidence of ulcer in all other types of disease was only 0·4 per cent. In more recent years the association between the two conditions appears to be less frequent, probably because fewer burns become septic, thanks to modern therapeutic methods. Of 115 subjects with burns included in 6800 autopsies investigated by Stewart (1923) only two had a peptic ulcer, one of these being a child of five years with a small ulcer of the pylorus.

Marasmus. Once the neonatal period with its special dangers is past, marasmus is generally regarded as playing a major etiological rôle in the production of ulcers in infancy (Holt, 1913; Gerdine and Helmholz, 1915; Paterson, 1922; Craig, 1934; Pfaundler and Schlossmann, 1935), though it is not always easy to decide whether marasmus is the cause or result of ulcer. It may be assumed, however, that in athreptic infants (and the same is true of those born prematurely) the gastro-intestinal mucosa tends to be thin and atrophic. Support for this belief is afforded by the work of Miller who, in the course of his investigation on gastric acidity, examined histologically a series of stomachs from infants dying in the first week of life and found that, as a general rule, the heavier the infant the better developed was the gastric mucosa.

Etiology obscure. Whilst the various factors discussed may all play an etiological rôle in peptic ulceration during infancy and childhood, this undoubtedly occurs at times without obvious cause. Birth trauma could be excluded in Craig's case of duodenal ulcer in a child born by Caesarean section. Marasmus is not invariably present, nor is there always a history of unsuitable feeding, since Berglund (1929) found peptic ulcers in eight infants exclusively or principally breast fed. Of his twenty cases five were in a good and three even in a very good state of nutrition. In seven of our nine cases there is no adequate explanation for the occurrence of the lesion. Four of these infants were moderately well-nourished, only three being marasmic. In no instance was there a history of difficult or prolonged labour. Feeding was fairly satisfactory, all the infants having been at least partially breast fed. The history is negative as regards sepsis except for a slight otitis media in one infant and nasal catarrh in another, and it is extremely doubtful whether an etiological rôle could be assigned to such trivial and banal infections. No noteworthy cerebral lesion was found in any of the seven brains examined, the slight superficial haemorrhage in one of these obviously being terminal. Of the two remaining cases ulcer was probably the result of drug irritation in one and of accident in the other.

External violence. This last case is of particular interest as it is extremely unusual to find peptic ulcer resulting from external violence. Perry and Shaw saw only two instances, both in adults, in 18,000 autopsies at Guy's Hospital. Single adult cases are also reported by Chalier and Desjacques (1923), and Hurst and Stewart respectively. The last-named authors also describe the occurrence of haemorrhages and superficial gastric erosions in cases of traumatic death, and consider that such lesions might be the starting point of ulcers should the patients survive.

Pathology of ulcers

Of the nine cases, eight were duodenal; in one instance both stomach and duodenum were involved. According to the general experience, duodenal preponderate markedly over gastric ulcers in childhood.

In Berglund's series of twenty cases, fourteen involved the duodenum, five the stomach and one both these structures. Burdick (1940) reports eight cases of peptic ulceration in a children's hospital, six duodenal and two gastric. Occasionally acute ulcers are found in other parts of the digestive tract in early life. Nixon and Fraser (1928) saw an ulcer at the cardiac orifice involving both stomach and oesophagus and they quote Henoch's neonatal case where a ring of ulceration encircled the lower end of the oesophagus. Meckel's diverticulum, according to Pfaundler and Schlossmann, may occasionally be the seat of ulcer in children, and Hurst and Stewart describe a heterotopic peptic ulcer of the lower ileum which gave rise to fatal haemorrhage in a child aged seventeen months. Rarely more than one child in a family may suffer from duodenal ulcer. Rogers (1928) reports its incidence in two consecutive infants in a family of three.

Duodenal ulcers, according to our experience and to that of others, invariably occur above the ampulla of Vater and are generally situated on the

posterior wall, the most dependent part of the bowel naturally coming into closest contact with the acid gastric contents before they are neutralized by the alkaline bile. One ulcer or more may be present. Holt found that about two-thirds of the reported ulcers were single. In the present investigation, one duodenal ulcer was present in three instances, two ulcers (one very small) occurred in a fourth, and three in two other cases. In another patient a single duodenal ulcer was combined with multiple gastric erosions, which, following the opinion of Hurst and Stewart, were regarded as superficial acute ulcers. In the final case of the series, the stomach and duodenum were not opened. The clinical diagnosis, however, based on repeated haematemeses was one of peptic ulcer. At operation a thickening which was felt beyond the pylorus was in all probability the result of a duodenal ulcer, and gastro-enterostomy was performed. The diameter of the duodenal ulcers in the present series varied up to 1·5 cm. All were acute with no appreciable thickening of the wall except in the operated case quoted above, and in one other of which the post-mortem report states 'the wall of the ulcer was firm with some apparent surrounding fibrosis'. In two instances all coats of the bowel were eroded, and the base of the ulcer was formed by the pancreas. In the two others the external coat, though adherent to pancreas, appeared to be intact and was probably torn at autopsy while separating the adhesions. In the remaining cases ulceration was more superficial and did not involve the whole thickness of the intestinal wall. No peritonitis was observed in any but the operated case where the slight recent inflammatory change found at autopsy was in all probability post-operative and not due to perforation. In four instances a fairly large eroded vessel was present in the base of the ulcer and partially clotted blood filled the stomach and bowel in three of them. Since the ulcers show no distinctive features as compared with adult lesion of similar type photographs have not been reproduced.

Histology

The ulcer was available for histological examination in three cases. Two of the ulcers had involved the whole thickness of the bowel wall with complete destruction of the muscle coats. The third was somewhat more superficial, although only the circular muscle remained intact. A striking feature in all was the absence of inflammatory reaction, the lesion being purely destructive with no attempt at repair. The microscopic appearances therefore support the view that such ulcers can develop rapidly and prove fatal before there is time for the occurrence of any noteworthy cellular reaction. There was no evidence of haemorrhage, old or recent, in any instance. Several fairly large arterioles were present in the immediate vicinity of the ulcer base in one case. Erosion of such a vessel could have given rise to severe haemorrhage. Gram-stained sections in each instance were examined for the presence of organisms with negative result. Other writers, like the author, are struck by the absence of any inflammatory reaction in these acute ulcers (Paterson, 1922; Selinger, 1932; Craig, 1934; Harkins, 1938; and others).

Clinical findings

Clinically haemorrhage from the stomach or bowel is generally considered the most important and characteristic sign of peptic ulceration in infancy, when symptoms, according to Burdick, are not typical as in adults. The characteristic ' hunger-pain ' is said not to occur before adolescence as a rule, nor can deep epigastric tenderness be elicited. Holt found that about one-third of the recorded ulcer cases were symptom-free during life, the lesion being discovered at autopsy in infants with marasmus or intercurrent disease. In a second group death occurred suddenly in collapse, sometimes preceded by ordinary gastro-enteritis. In this type of case autopsy sometimes showed concealed intestinal haemorrhage, death having occurred before the actual passage of blood. In a third group the ulcer perforated and led to peritonitis.

Six patients of the present series gave a clue to the presence of ulcer during life by haematemesis or melaena. Haemorrhage was severe in four, moderate in one and slight in one. In the other three there was nothing in the clinical picture to suggest the presence of peptic ulcer. In one of the latter there had been persistent vomiting and marasmus and the child died after several convulsions. In a second the condition appeared to be ordinary gastro-enteritis. The third, who was admitted on account of an irreducible inguinal hernia, collapsed suddenly and died. The prognosis of peptic ulcer in infancy is poor owing to the frequency of gross haemorrhage which is ill-borne. Rarely, however, such ulcers appear to heal spontaneously; thus Gerdine and Helmholz (1915) saw an ulcer practically healed in an infant aged three months, and in Harrison's case quoted above, though the presence of peritonitis indicated perforation, the duodenal ulcer had actually closed.

Complications

Complications such as haemorrhage and peritonitis, appear from the literature to be fairly common in infants, probably on account of their delicate gastro-intestinal wall. Perforation is reported by Craig in a baby aged six days. Finny (1908–09), Somerford (1930), and Harrison (1931) saw peritonitis associated with perforated duodenal ulcer in slightly older infants, and Firmin-Edwards (1941) describes the rupture of a gastric ulcer with escape of stomach contents in a child of six months with hepatic cirrhosis. Peritonitis is generally afebrile since the duodenal contents are normally sterile and inflammation of the peritoneum is due to mechanical irritation rather than to infection.

Differential diagnosis

In the past severe neonatal intestinal haemorrhage has generally been attributed to melaena neonatorum, a term signifying generalized capillary oozing from a mucosa showing no gross defect. In such cases, however, careful post-mortem examination might sometimes have revealed ulceration. Hurst (Price, 1941) states that acute duodenal ulcer is the most common cause of melaena neonatorum. With this opinion we are unable to agree, as in this hospital many instances of copious intestinal haemorrhage have been seen

although gross ulceration of the gastro-intestinal tract has been excluded by careful search in such cases.

Should peptic ulcer cause spasm of the pylorus, hypertrophic pyloric stenosis may be simulated, and several cases of this type have been reported (Finny). In the case recorded by Brockington and Lightwood the passage of barium through the pylorus was delayed in an infant with a peptic ulcer. Holt thinks the association of pyloric spasm and duodenal ulcer too frequent to be accidental. The occurrence of haematemesis or melaena in a young infant whose condition is otherwise suggestive of pyloric stenosis should suggest the possibility of peptic ulcer. In diagnosis other causes of intestinal haemorrhage such as intussusception, colitis, rectal polyps must also be taken into account.

Chronic peptic ulcers in children

Though the vast majority of peptic ulcers in children are acute, chronic ulcers being extremely rare before puberty according to Hurst and Stewart, a few verified cases of the latter are recorded. Paus (1926–27) saw a chronic lesion in two children aged respectively nine and fourteen years, each with a long history of digestive trouble. Theile (1919b) reports a chronic ulcer verified at operation in a child at the early age of two years, as well as two further examples in adolescents aged thirteen and fifteen. Jankelson (1932) adds three further cases with characteristic x-ray findings, two at twelve years, the third at ten. Proctor's case of indurated ulcer with repeated acute exacerbations has already been mentioned. Such proved instances of chronic ulcer originating in childhood, sometimes even in the first few years of life, are of particular interest in view of the fact that some adults with peptic ulcer date their symptoms back to early childhood. Proctor, at the Mayo Clinic, traced the records of 1000 patients with gastric and 1000 with duodenal ulcer. Among the former sixteen, and among the latter twenty-six, had symptoms dating back to childhood. Henderson (1930–31) and Hurst and Stewart also quote adult cases with symptoms of digestive disturbance of many years' duration. More recently confirmation of early onset of some peptic ulcers has been afforded in the course of mass investigation of young soldiers with dyspepsia (Tidy and others, 1941). Judging from the scanty records of chronic ulcer in children, the results of operation are good (Theile, Paus). Jankelson's cases improved with dieting. Malignant change does not appear to have been described in juvenile ulcers.

Summary

From our own and others' findings it is evident that peptic ulceration is a well authenticated though rare disease of infancy and childhood, occurring at all ages from the first day of life onward. The youngest patient in the present series died at the age of three days. All the present cases with one exception were infants under the age of six months, and it is common experience that the majority of infantile peptic ulcers occur in the early weeks of life. Such ulcers are believed to originate after birth. The delicacy of the gastro-intestinal wall

in the new-born probably suffices to explain their rapid development. Distribution is approximately equal in both sexes. The present nine examples are included among 6059 autopsies (incidence 0·14 per cent.), approximately two-thirds of which were on children under the age of one year. On comparing these figures with those of others in child populations of approximately similar age distribution, Holt's in the Babies' Hospital, New York, most closely approach the Glasgow series. He found four duodenal ulcers in 1800 autopsies (0·22 per cent.). Paterson saw two examples among 566 post-mortems at Great Ormond Street, but mentions that no single case had occurred there in the previous twenty years. Berglund's incidence (1·55 per cent.) in Stockholm is considerably higher than our own, twenty peptic ulcers including one of tuberculous nature occurring in his series of 1323 autopsies. Frequency may vary according to locality, or if there are at times small epidemics of such ulcers associated with infection (Gerdine and Helmholz), distribution from year to year would tend to be uneven. Certain circumstances incidental to birth and early infancy are invoked to explain the frequency of peptic ulcer at this age. Thus it is believed that circulatory instability especially in prolonged labour tends to devitalize the duodenal mucosa, any damaged area then being liable to digestion by the gastric juice, which, according to Miller, has a remarkably high acidity in the first forty-eight hours of life. Direct trauma to the gastric mucosa may occur accidentally during resuscitation at birth, whilst congestion and possibly haemorrhage may result from hyperperistalsis associated with congenital duodenal stenosis. Further, umbilical sepsis may play an etiological rôle in the newborn. In early as in later infancy, mucosal irritation may be produced by drugs or by unsuitable feeding. In babies past the neonatal period marasmus is the condition most frequently associated with peptic ulcer. Here the gastro-intestinal mucosa is probably thin and atrophic and hence less resistant than usual to the digestive action of the gastric juice. Divers types of infection may lead to ulceration. Meningitis would appear to be of particular importance in this respect. Sometimes there is no apparent etiological factor, as in the majority of the present cases (seven). Of the other two external violence was considered responsible in one, and drug irritation in the other. Eight of the ulcers in the present series were duodenal, one gastro-duodenal. The preponderance of duodenal over gastric ulcers in childhood is confirmed in the literature. Parts of the gastro-intestinal tract other than the stomach and duodenum are rarely affected, ulcer then originating in islets of heterotopic mucosa.

Duodenal ulcers in our experience and in that of others occur almost exclusively above the ampulla of Vater on the posterior wall. They are generally single though at times two or more may be present. They do not generally greatly exceed 1 cm. in diameter and may be much smaller. The ulcer in several of our cases had eroded all coats of the intestine so that the base was formed of pancreatic tissue. In four instances a large eroded vessel was present in the base of the ulcer and in three of these the stomach and bowel were filled with blood. No peritonitis was observed in any of the present cases, though this appears to be a fairly frequent complication especially in infants.

On histological examination of such acute ulcers the lesion as a rule is purely destructive, the absence of a cellular response suggesting a rapidly fatal evolution before the defence mechanism has time to come into play.

Clinically haemorrhage from stomach or bowel is the most characteristic sign of peptic ulceration in young children in whom ' hunger-pain ' and epigastric tenderness are generally absent. In six of the present nine cases haematemesis or melaena had occurred during life. Haemorrhage may be the initial feature, or it may be preceded by dyspepsia. Again, the child may collapse in the course of an apparently simple gastro-enteritis and die from concealed haemorrhage, or the lesion may remain clinically latent till perforation and peritonitis supervene. In the absence of haemorrhage, ulcer is generally unsuspected, as in three of the present cases.

Duodenal ulcer may at times cause spasm of the pylorus when the condition may suggest hypertrophic pyloric stenosis. In an infant with symptoms otherwise characteristic of the latter condition haemorrhage from the stomach or bowel should suggest the likelihood of peptic ulcer. Not only acute but even chronic indurated ulcers have been recorded in children. The fact that some adults with peptic ulcer can trace their symptoms back for many years confirms the possibility of juvenile onset. Wide recognition of the possibility that chronic ulcers may arise in childhood is greatly to be desired in order that prompt relief may be afforded by suitable treatment.

Summary of case histories

Case 2, M. P., female, aged three days, was born after a normal, full-time pregnancy on July 26, 1930 (hour of birth not stated) and was admitted on July 28 with the history of having been well till 3 p.m. on that day when haematemesis and melaena occurred. The haemorrhage recurred in hospital despite intraperitoneal injections of blood, and the infant died at 6 a.m. on July 29. The disease, therefore, first manifested itself about forty-eight hours after birth. At autopsy, the stomach showed multiple small sharply-defined circular erosions and contained abundant blood-clot. In addition a terraced duodenal ulcer with an eroded artery in the base was present about $\frac{1}{4}$ inch beyond the pylorus. The whole bowel was filled with blood clot. The abdominal and thoracic viscera were free from disease. The head was not examined.

Case 3, W. E., male, aged seventeen weeks, was admitted on August 18, 1927, sunken and depleted with a history of vomiting and fever of ten days' duration. He was born after a normal, full-time pregnancy and appeared healthy. Breast milk had been given for one month, thereafter diluted cow's milk. On August 22 bright red blood was passed per rectum on several occasions. Death occurred on the following day. At autopsy the slightly dilated stomach contained ' coffee-ground ' material. In the first part of the duodenum was a small ulcer with a haemorrhagic base. The bowel showed no other lesion. The abdominal and thoracic organs and the brain were healthy. Both middle ears contained a little pus.

Case 4, male, aged three months, born after a normal, full-time pregnancy, was admitted on May 30, 1926. He was small and much emaciated. He had been healthy at birth (weight 10 lb.). After receiving breast milk for a fortnight the feed was changed to diluted cow's milk. He failed to thrive, lost

weight steadily and was very cross. There was no diarrhoea or vomiting. Two days before admission he had repeated convulsions. Intraperitoneal saline and blood transfusion were without effect and the child died on June 1. At autopsy, a little ' coffee-ground ' material was present in the stomach. A duodenal ulcer ½ inch in diameter was present about 1 inch beyond the pylorus. Its walls were firm with some apparent surrounding fibrosis. The base of the ulcer was formed by the pancreas. About ½ inch farther along the duodenum a second smaller superficial ulcer was discovered. No other intestinal lesion was found and there was no gross morbid change in the thoracic or abdominal organs. The brain substance was normal except for slight oedema. Some of the meningeal veins were thrombosed with slight subdural and subarachnoid haemorrhage.

Case 5, A. F., male, aged eleven weeks, was admitted in an emaciated state on December 3, 1937, with a two days' history of frequent vomiting and green diarrhoea. A right inguinal hernia was present which was at once reduced under anaesthesia. On December 12 the child looked very pale, collapsed suddenly and died. At autopsy the gastric mucosa was engorged. The duodenum which was moderately congested showed three small ulcers in the first part. The largest and deepest, about ½ inch in length, was situated immediately beyond the pylorus. The ulcer had perforated the muscle, but the serosa was intact. The other two ulcers were smaller and superficial. Marked mucosal congestion was present in the rest of the bowel. The thoracic and abdominal viscera and the brain were healthy. Muco-pus was present in both middle ears. The ulcer was examined histologically when the lesion was purely destructive, all coats of the bowel having been eroded without any attempt at repair. No organisms were seen in Gram-stained sections and haemorrhage was absent.

Case 6, I. C., female, aged six months, born at term after a normal labour, was admitted on December 17, 1917, with a complaint of vomiting and nasal catarrh since birth. She had been breast fed for four months; various artificial feeds had subsequently been tried without improvement. On several occasions the vomitus was of ' coffee-ground ' type. On admission the child was pale and thin with a distended but lax abdomen, showing no peristalsis. Several attacks of haematemesis occurred in hospital, bright red blood having been brought up on one occasion. On December 22 the abdomen was opened, when a thickening was felt just beyond the pylorus and gastro-enterostomy was performed. Death occurred four days later. At autopsy slight recent peritonitis was present and the left lung showed a patch of broncho-pneumonia. The stomach and duodenum were preserved intact as a specimen but could not be traced. There is no note of the findings, hence the diagnosis of peptic ulcer in this case rests on the clinical findings which were pathognomonic.

Case 7, J. D., male, aged five weeks, born at term without chloroform or instruments, was admitted on October 2, 1941, moderately jaundiced, anaemic and wasted. Icterus had been present for the previous ten days and the child had been losing weight steadily. Two dark-coloured motions were passed shortly after admission. These gave a positive guaiac reaction. Death occurred two days after admission. At autopsy the liver which was dark-green showed no cirrhosis, jaundice evidently being of catarrhal type. The right and left hepatic ducts were patent and a probe passed readily along the common duct formed by their union and emerged at the ampulla of Vater, which was blocked by thick mucus. The gall-bladder was a small collapsed structure containing similar material. Its minute duct was quite impermeable to the passage of a probe. In the first part of the duodenum on the posterior wall

three small ulcers were present, the largest and deepest measuring 0·2 by 0·15 inch. The other two were very small and superficial. The duodenal mucosa was moderately congested. A small amount of altered blood was mixed with the contents of the lower ileum. Nothing of note was found in any of the abdominal viscera and the brain was healthy. The right lung was the seat of diffuse broncho-pneumonia. On microscopic examination the ulcers had not invaded the entire thickness of the duodenal wall; the longitudinal muscle coat was partially eroded, but the circular muscle was intact. The inflammatory reaction was negligible. No organisms were seen in sections stained by Gram's method.

Case 8, E. McA., female, aged ten weeks, born at term, was admitted on March 9, 1914, with a history of frequent non-expulsive vomiting since birth. She had been breast fed for one month; subsequently various artificial foods had been tried without improvement and she appeared to be often in pain. Large doses of oleum ricini were given during the first two weeks of life. The condition did not improve and death occurred on March 16 after several convulsions. At autopsy an ulcer $\frac{1}{4}$ inch in diameter was present on the posterior wall of the duodenum immediately beyond the pylorus. The state of the other organs is not described nor does the report state whether blood was present in the gastro-intestinal tract.

Case 9, C. C., female, aged six years, was admitted on December 22, 1922, as an accident case (nature unspecified) in a condition of profound shock. x-ray examination revealed a right-sided pneumothorax. On December 27 blood was passed per rectum for the first time. Haemorrhage recurred on December 27 and 28 despite intramuscular injection of blood and of horse serum. Death occurred on December 29. There was no history of any previous gastric trouble, the child having been in good health prior to the accident. At autopsy the right lung was torn and haemopneumothorax was present. Immediately beyond the pylorus was a large duodenal ulcer adherent to the head of pancreas. In its base was found a small bleeding vessel, the source of the blood which filled the stomach and bowel.

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CASE REPORTS

TWO CASES OF DUODENAL ULCERATION IN CHILDREN

BY

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A growing number of articles (Paterson, 1922; Proctor, 1925; Kennedy, 1933; Craig, 1934; Mills, 1934; Burdick, 1940) show that peptic ulceration in children is not regarded seriously enough as a cause for puzzling gastro-intestinal symptoms. The admission of two cases of duodenal ulcer into a children's unit within a period of six months forms the occasion for this report.

Two groups of cases are likely to be met, a first broad division separating a 'primary' type in which the ulcer and its effects fill the foreground of the clinical and pathological picture, and a 'secondary' type, to be discussed no further, in which an ulcer develops in a child already suffering from some serious condition such as gastro-enteritis, peritonitis or a general infection.

Kennedy (1933) has classified the 'primary' cases into four with well-defined age incidence—neonatal, from a few weeks to twelve months, from one to nine years, and an adult type in later childhood. Cases since reported fit into this scheme.

Types of 'primary' ulceration

Neonatal type. In that miscellany of pathological conditions dubbed haemorrhagic disease of the newborn, gross melaena and haematemesis may arise from a bleeding ulcer. When death results from blood loss or from peritonitis following perforation, a large ulcer may be found. In one fatal case Kennedy (1924) reported microscopic ulceration of the duodenal mucosa where no macroscopic lesion was visible. If this is pathologically acceptable, recovery can be expected in some cases, and diagnostic difficulty in all, since a barium skiagram of stomach and duodenum would be normal and an autopsy without serial sections misleading. When there is serious bleeding from the gut with anaemia, without enlargement of spleen or liver and without erythroblastosis, peptic ulceration is a possible diagnosis, and treatment directed against the bleeding and the anaemia should be with vitamin K and repeated blood transfusions.

Infantile type. The diagnosis is rarely made until the onset of haemorrhage, and usually not until the post-mortem examination. A certain resemblance

between reported cases and case 1 shows that there are suggestive features in the history. A good start with feeding and weight gain is interrupted at the age of a few weeks or months by an infection, especially of the upper respiratory tract. Thereafter failure to thrive is associated with feeding difficulty, and there is unwillingness to take or to finish feeds, natural or artificial, with vomiting if feeds are pressed, and attacks of abdominal pain or discomfort. Changes in feeding may cause temporary improvement. The mother is accused of over-anxiety. In case 1 anxiety was increased by the laryngeal stridor which she understood to be due to a growth in the larynx capable of suffocating the baby at any moment. After further infections comes the terminal stage of bleeding, often mistaken for acute intestinal obstruction and treated by exploratory laparotomy. Whether or not parenteral blood and fluids with sedatives and alkalis by mouth would avert a fatal issue remains to be seen.

Childhood type. In children of between one and nine years vague gastro-intestinal symptoms, loss of appetite, failure to gain weight, if accompanied by abdominal pain, especially in the upper abdomen, or by epigastric tenderness, or by anaemia, should suggest an ulcer. Here again in many cases there is upper respiratory infection, and, in case 2 there was also evidence of psychological disturbance, with an unusually difficult domestic background. Without obvious or occult bleeding from the gut, or radiographic proof of an actual ulcer, the diagnosis is open to grave doubt. The statement of Moore (1941) that ' though desirable the demonstration of a crater is not always possible or necessary ' may only confuse still further the already difficult subject of chronic gastro-intestinal disease in childhood. Fractional test meals are not apparently of value.

When the case presents as one of anaemia with gastro-intestinal symptoms and bleeding from the gut the differential diagnosis is from a bleeding ulcer in relation to ectopic gastric mucosa, ulceration from tuberculosis of the bowel, and intestinal polyps or parasites. Malignant neoplasms of the gut are exceedingly rare in the age period under discussion. In bleeding from an ulcer in a Meckel's diverticulum anaemia is characteristically acute and severe, and there is abdominal discomfort more than pain, without local tenderness. Appetite remains good throughout, there is no vomiting or haematemesis, weight gain is not affected. There are no symptoms between attacks. Diagnosis may be made by special barium meal examination or by laparotomy.

Adult type. In the later childhood years peptic ulceration produces a picture resembling that in adults.

Case reports

The following two cases represent the infantile and the childhood types.

1. D. B., male, born 1/3/41, was admitted to hospital 17/7/41 and died 8/8/41 (aged 5 months). Birth was three weeks early, but otherwise normal, and birth weight was 6 lb. 12 oz. He seemed healthy, although jaundiced from the first to the twenty-first day. Breast feeding was established and progress was good until the age of four weeks, when he had a ' cold ' with nasal discharge and a cough. He was unhappy, refused feeds, slept badly, cried much and

became difficult to handle. At six weeks he was weaned on to a 'humanized' dried milk (2½ level teaspoons in 3 oz. with ½ level teaspoon of glucose, three-hourly). At eleven and a half weeks (21/5/41) he was taken to a clinic where the feed was changed to a half-cream dried milk (5 oz. feeds four-hourly with later addition of 1 level teaspoon of glucose to each). His weight was then 10 lb. 7 oz., giving an average gain of over 6 oz. a week from the second week. This proved the maximum recorded weight. A vitamin A and D concentrate was added on 4/6/41 and on 18/6/41 the feed was changed again to another humanized dried milk (4 scoops to 5 oz. four-hourly). With each change he improved, but soon would lose his appetite and either vomit after or regurgitate curds between feeds. He would begin the feed with gusto, taking the first two or three ounces greedily, and then would take slowly and with much persuasion. The average time was half an hour varying from twenty minutes to one hour. Bowels were opened normally until 7/7/41, when he began green frothy motions, three or four each day. The strength of the feed was lowered to three scoops in five ounces and the motions improved.

Breathing had been noisy from birth, worse since the 'cold.' A loud croaking accompanied inspiration and expiration, the intensity varying, almost disappearing at night, becoming worse after feeds. Respirations were never laboured nor rapid, and he was never blue.

Examination on admission (17/7/41). A four months' old well baby, with mucous membranes of good colour, not cyanosed. Weight 10 lb. 4½ oz. Laryngeal stridor is present, and is unaffected by change of position of the head. There is suprasternal inspiratory recession but normal expansion of the lower ribs. Skull normal and general examination otherwise normal.

Diagnosis. Congenital laryngeal stridor; feeding difficulty associated with over-anxious mother and poor management (gross libels as was later apparent).

Progress was at first good. He was fed part separated and part full cream dried milk with added sugar, 5 oz. four-hourly ($\times 5$). The separated milk was gradually reduced and the sugar increased, but after eight days (25/7/41) motions increased to six and were looser, so that sugar was reduced. He began to vomit 29/7/41, temperature rose to 99·8° F., and pulse to 150, and thereafter he refused feeds, which were reduced in strength until on 31/7/41 he was put on to boiled water. Later in the day he was dehydrated and was given a slow sub-cutaneous injection of normal saline (300 c.c.). A left myringotomy for a red bulging drum produced blood-stained fluid, but on the next day a discharge of pus. Though there was slight improvement, he remained a sick baby with irregular fever (up to 100° F.), poor appetite, vomiting if feeds pressed, and one to three stools a day, not particularly loose. No non-lactose fermenting organisms were grown on stool culture. Two stools were streaked with dark blood and some mucus on 7/8/41, and later he looked ill, frowning as if in pain, the abdomen being soft, not distended, and tender over the right upper quadrant, where the liver was enlarged to two fingers breadths. In one vomit was a small streak of bright blood. Stool culture, repeated, was negative, and blood count showed Hb. 94 per cent., R.B.C. 4,880,000 per c.mm., W.B.C. 31,600 per c.mm. 8/8/41 at 3.0 a.m. he passed much bright blood without faeces per rectum. At 5.30 a.m. he was moaning and frowning in pain, T. 97° F., P. 130, R. 36.

He appeared extremely ill, with upper abdominal distension and tenderness under the liver edge. No tumour was felt, but as no faeces had been passed for twenty-four hours, and there was distension, pain and bleeding from the gut, a diagnosis of intestinal obstruction was made, possibly due to intussusception. At operation (Mr. J. P. Hosford) a clear fluid was found in the peritoneal cavity. The small intestine and colon up to the hepatic flexure

were distended and contained dark fluid. No obstruction and no Meckel's diverticulum could be seen. The baby died twelve hours later.

Post-mortem examination (Dr. Joan Ross) revealed a wide duodenal ulcer on the posterior wall with an eroded vessel in the base. There was altered blood in the duodenum. The liver was yellow, necrotic, and greatly enlarged, and showed in sections intense fatty degeneration, only a few cells being recognizable. The kidneys showed cloudy swelling. The larynx did not differ from that of a normal baby of the same age, and on section the ary-epiglottidean folds appeared normal.

2. A. P., male, unaccompanied evacuee, born 9/3/32, was admitted to Cell Barnes Hospital 21/1/41 from his billet on account of dizziness and abdominal pain. He had been sent home from school as he was dizzy, felt sick, had sharp upper abdominal pain and a bad appetite.

He was born at term, weighing 7 lb. 2 oz., and was blue for two weeks. After two weeks of breast feeding he was fed artificially without cod-liver oil, but with orange juice. He had nasal catarrh and attended the Belgrave Hospital. At one year he was admitted to Lambeth Hospital for pneumonia, later to St. Giles' Hospital with chest trouble, then to Goldie Leigh and Homerton with chickenpox. He was always in and out of hospital, sometimes with cough and chest trouble, sometimes on account of sickness. He used to have poor appetite, would be coaxed and then would vomit at table. There were always rows over meals and his mother lost her temper and smacked him. He had some abdominal pain, at first attributed to constipation and treated with paraffin. He always liked meat and milk but not vegetables; he took eggs and butter, but was not fond of fried food.

October 1938, as he was pale and had bronchitis, he attended St. Thomas's Hospital for sun-ray. He made no progress, and 23/11/38, aged 6½ years, he was admitted to Lambeth Hospital on account of sore throat and purpuric spots on legs. (Blood count Hb. 68 per cent., R.B.C. 4,230,000 per c.mm., W.B.C. 10,000 per c.mm. Normal differential count.) Progress was satisfactory until ' 19/10/38, when he vomited blood-stained matter and his haemoglobin fell to 32 per cent. He was given a blood transfusion and treated as if he had a peptic ulcer. A platelet count at this time was normal. There is no record of a barium meal examination. The diagnosis made on discharge was follicular tonsillitis and haematemesis (probably due to a peptic ulcer).' (P. J. Watkins, Medical Superintendent 8/3/41). Since then he has been in fair health except for poor appetite until just before admission, although he confessed to occasional upper abdominal pain unrelated to meals or exertion. Latterly he has felt a little dizzy and short of breath on exertion.

He sleeps well, became clean and dry early and without difficulty. Measles at 2 years. Chickenpox at 5 years.

Domestic history. The mother lived with his father for only six weeks and then left him. He knows of his real father but has seen him seldom. In 1934 the mother married again, and the stepfather gets on well with the boy. There was a miscarriage at six or seven months in 1938. There has never been a settled home: at first mother and baby lived with mother's mother and mother worked. Later mother left him entirely with grandmother but would have him with her for occasional weekends. At other periods he has been in charge of a foster mother, and then on many occasions in various hospitals. Mother does not think she was missed. Mother's sister was fond of him: she had pneumonia and pleurisy and had an operation, after which she died suddenly in June 1940. Shortly after mother's father died. The boy was strongly attached to both and was extremely upset. Then the ' blitz ' started and he was evacuated to St. Albans.

On examination. Pale, ill boy with yellow tint of skin. Mucous membranes markedly pale. Sclerotics not yellow. (T. 99° F., P. 100, R. 24.) Weight 65½ lb. Eyes and fundi normal. Teeth good. Tonsils large, not inflamed. No enlarged lymph nodes. Systolic murmur at base of heart but otherwise normal. Blood pressure 106/60 mm. Hg. Abdomen soft, liver and spleen not enlarged. No tenderness, no tumour. Limbs normal. Urine clear, no albumin, no blood, no abnormal pigment. Stool formed, dark and contains obvious altered blood. Wet films showed R.B.C. in considerable numbers. Afebrile, ill, lassitude, anorexia.

After about a month general condition improved greatly and appetite became good.

Investigations:

22/1/41 R.B.C. 2,340,000 per c.mm. Hb. 48 per cent. (6·62 gm.). C.I. 1·12. W.B.C. 7000, polymorphs 4760 (68 per cent.), eosinophils 70 (1·5 per cent.), basophils 70 (1 per cent.), lymphocytes 1750 (25 per cent.), mononuclears 350 (5 per cent.), aniso- and poikilocytosis, and polychromasia. No nucleated cells.

25/1/41 Reticulocytes 2·4 per cent. Fragility of R.B.C.: haemolysis begins at 0·45 per cent., complete at 0·4 per cent. Fouchet negative. Van der Bergh direct negative. Indirect less than 0·4 units.

25/1/41 Wassermann, Kahn and Meinicke Reactions negative.

26/1/41 Occult blood (Benzidene) strongly positive.

27/1/41 ,, ,, ,, negative.

31/1/41 Bleeding time: 1 min. 30 sec. (Duke).
Coagulation time: 6 min. (Lee and White 4–7 min.).
Reticulocytes 2·4 per cent.
Platelets 196,000 per c.mm.
R.B.C. 2,640,000 Hb. 50 per cent. (6·9 gm.), C.I. 0·94.

12/2/41 R.B.C. 3,660,000, Hb. 70 per cent. (9·7 gm.), C.I. 0·97.
Reticulocytes 2·5 per cent.

1/4/41 Occult blood: 3 specimens positive.

19/5/41 R.B.C. 4,740,000, Hb. 84 per cent. (11·6 gm.), C.I. 0·89.
W.B.C. 9500.

24/5/41 Fractional test meal (7 per cent. alcohol) 30 c.c. at 11.50 a.m.

	2/10 HCl	FREE HCl GM. PER CENT.	TOTAL ACIDITY		BILE	MUCUS
			2/10 HCl	GM. HCl PER CENT.		
Resting juice ..	36	0·131	60	0·219	0	0
12.05 0	23	0·084	40	0·146	0	0
.40 35 minutes ..	0	0	19	0·069	0	0
1.15 70 minutes ..	22	0·080	40	0·146	0	0
	No blood No starch					

Radiography (reports by Dr. G. Simon)

26/1/41 Plain abdomen: normal.
AFTER BARIUM—stomach shows normal peristalsis and emptying.
Duodenum: fairly gross deformity of the duodenal cap with projection. Diagnosis: duodenal ulcer.

20/2/41 AFTER BARIUM: Stomach still contains fluid (last food 12 hr. before). There is deep peristalsis with intermittent emptying.
Duodenum: There is still deformity of the cap with projections. The ulcer crater does not appear to be healed.

24/3/41 AFTER BARIUM: Deformity of the duodenal cap is present as previously, in fact a small diverticulum appears to be forming near the lower part of the cap (fig. 1).

20/5/41 Duodenal cap now smooth and regular in outline. The ulcer crater appears to have healed.

FIG. 1.—24.3.41. At A pseudo-diverticulum of the duodenal cap.

Intelligence tests (Dr. Millman): Showed a high standard of mental ability in all the tests used.

Psychological examinations: May, 1941 (Dr. Lovel Barnes):

'In examining this child I endeavoured to estimate two important problems: (*a*) was there an emotional factor in the commencement of his illness; and (*b*) to what extent his progress was influenced by his psychological condition. I found it extremely difficult to form an estimate of (*a*). It was necessary to work back from the state in which I found the child to-day and a subsequent interview with the mother did not clarify the position. With regard to (*b*) I considered that he was an intelligent but insecure child. There was a considerable amount of anxiety about his illness which he managed to cover to quite an extent. The anxiety, however, did not all centre on the illness; a great deal of it was concerned with the idea of separation from his mother and could be considered a true separation anxiety. In my interview with the mother this was discussed and I was so impressed by the importance of it that I agreed to the mother taking the child back to Clapham (although he was exposed to the risk of air raids) rather than produce further anxiety by a prolonged separation. It is evident, therefore, that there is considerable emotional instability in this case which has obviously been there since early childhood. It is now undoubtedly influencing his health, and it cannot be disregarded as a possible precipitating cause although there is of course no proof of this. I do consider, however, that it would play a strong part in producing a recrudescence of the symptoms at a future date.'

Treatment. Bed for ten weeks on post-Lenhartz diet with ascorbic acid 50 mgm. and a vitamin A and D concentrate, 15 minims a day and liquid paraffin, 30 minims, three times a day after meals. Two tablets of iron sulphate twice a day from 4/2/41.

Weight on discharge was 70 lb.; he was eating well. Since then he has been free from symptoms, and weight (6/3/42) at ten years is 81 lb. He has been living with his mother but attends school regularly.

Summary

Two cases of duodenal ulcer are reported in detail. One (infantile type) died at five months. The other (childhood type) bled first aged 6½ years, was diagnosed at 8 years 10 months, and made a good recovery.

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FOUR CASES OF DUODENAL ULCERATION IN CHILDREN SIMULATING ACUTE APPENDICITIS

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The general impression in this country appears to be that duodenal ulceration is an extremely rare condition in childhood. Recent experiences do not entirely corroborate this opinion, as duodenal ulceration has been diagnosed in young children in no fewer than four cases during the past year at one Emergency Medical Service Sector Hospital.

All these patients were sent into hospital as cases of acute appendicitis and this diagnosis appeared correct clinically. An accurate history was difficult to obtain in such young children; the presence of a temperature, a raised pulse, a furred tongue, pain and tenderness in the right iliac fossa made laparotomy imperative. The removal of normal appendices suggested that further investigations were desirable. Accordingly fractional test meals followed by barium meal examinations were carried out in each case, with results which will be discussed.

Case reports

Case 1. B.M., a boy, aged five years, was admitted with a history of acute central abdominal pain, which had started twelve hours previously. Later, during the day, the pain was referred to the right iliac fossa. There was no

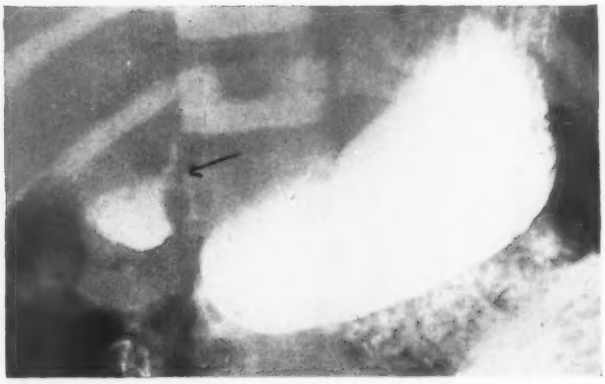

FIG. 1.—Case 1.

nausea or vomiting. For several days the child's appetite had been poor; there was no history of constipation or diarrhoea.

On Examination.—Temperature 100·6° F.; pulse 116. Child answered questions sensibly and did not look very ill. There was generalized guarding all over the abdomen with marked tenderness in the right iliac fossa, the right loin and the upper part of the right groin. Chest and urine examinations revealed no abnormality. Laparotomy was performed, but as the findings were inconclusive it was decided to continue investigations. Owing to the child's age it was not considered practicable to perform a test meal; investigations in this case are limited to a barium meal and are therefore incomplete. Barium meal result (fig. 1): 'The stomach is normal in appearance; it does not empty as rapidly as it should, there being a slight residue at six hours. The duodenal cap shows distinct signs of ulceration, and in view of the absence of abnormality elsewhere, this must be the diagnosis.'

Treatment was then continued on medical lines for four weeks, the child's symptoms subsiding completely after a few days.

Case 2. S.M., aged thirteen years, was admitted with the diagnosis of acute appendicitis, with a vague history of pain in the right iliac fossa. Temperature 99° F.; pulse 100. No tenderness on examination. Rectal examination: nothing abnormal detected. Chest and urine: no abnormality. Operation was not considered necessary. On the following day, however, the temperature rose to 100·4° F., with a pulse rate of 110, and there was definite rigidity and tenderness in the right iliac fossa. There was still no tenderness per rectum. Operation was now considered advisable, but a normal appendix was found.

The following investigations were performed: Chest x-ray: no abnormality. Leucocyte count 11,000 per c.mm. Urine: no crystals, casts or organisms.

Fractional test meal (fig. 2).—Resting juice 83 c.c. with a total acidity of 45 on the Ewald scale (i.e. 0·16 per cent. HCl). Free HCl was 30, equivalent to 0·1 per cent. HCl. The total acidity fell to 5 after half an hour when the

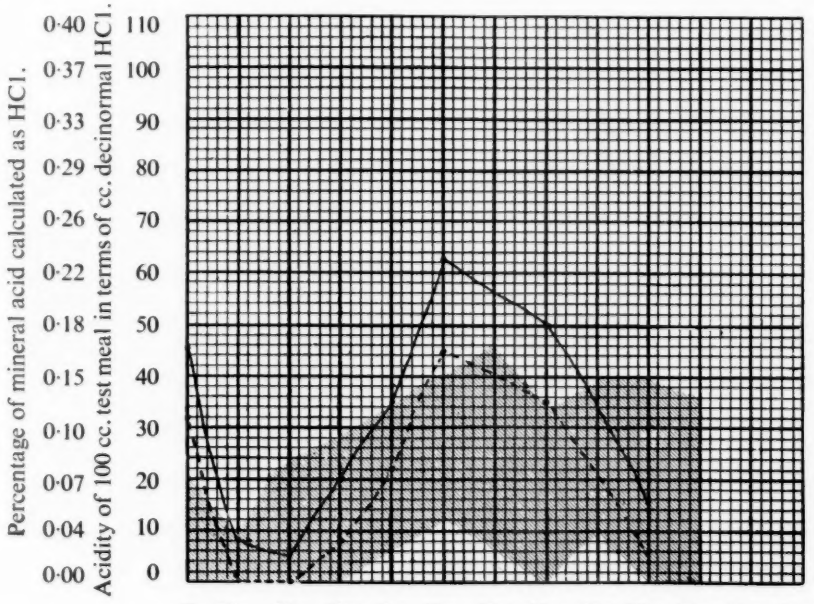

Fig. 2.—Case 2.

free HCl content was nil. Both acidity curves rose steeply and at 1¼ hours reached a maximum of 65 and 45 respectively. The readings fell equally rapidly to 15 and 5 after 2¼ hours. A microscopic examination of the resting juice revealed a few squamous epithelial cells and also a few partly digested pus cells. Traces of mucus were present in the resting juice, and after one hour. Starch was still present after 2¼ hours. Bile appeared after 1¾ hours. Blood was absent throughout.

BARIUM MEAL (fig. 3) showed a normal stomach. The duodenal cap failed

FIG. 3.—Case 2.

to fill but was not tender. The appearances strongly suggest recent duodenal ulceration.

After three weeks of intensive medical treatment the barium meal was repeated, and it was found that the deformity of the duodenal cap still persisted.

Case 3. B.H., a boy, aged seven years, was admitted with symptoms simulating acute appendicitis. He had vomited once on the same day, having lost his appetite several days before admission. On admission the temperature was 102·2° F., and the pulse 130. He also complained of pain on micturition, but was not tender in the loins or over the bladder. He was, however, rather tender per rectum on the right side. The urine and chest showed no abnormality. He looked flushed, his tongue was furred and he seemed to be in great distress. Examination of the abdomen revealed marked tenderness in the right iliac fossa, and epicritic sensibility was increased on the right side of the abdomen.

Laparotomy was performed, and in view of the negative findings, once again further investigations were deemed necessary.

Leucocyte count: 17,000 per c.mm. Sedimentation rate 24 mm. per hour. Chest x-ray negative. Urinary culture and guinea-pig inoculation showed no organisms or tubercle bacilli. Benzidine test for occult blood and spectroscopic examination were negative.

FRACTIONAL TEST MEAL (fig. 4).—The resting juice was 19 c.c. with a total acidity of 11 (i.e. 0·03 per cent. HCl) and no free HCl present. The maximum

rise occurred after 1¼ hours, namely 35 and 20 respectively, and these levels were maintained until 2¼ hours. Microscopy revealed a few squamous epithelial cells and a fair number of partly digested pus cells. Starch was

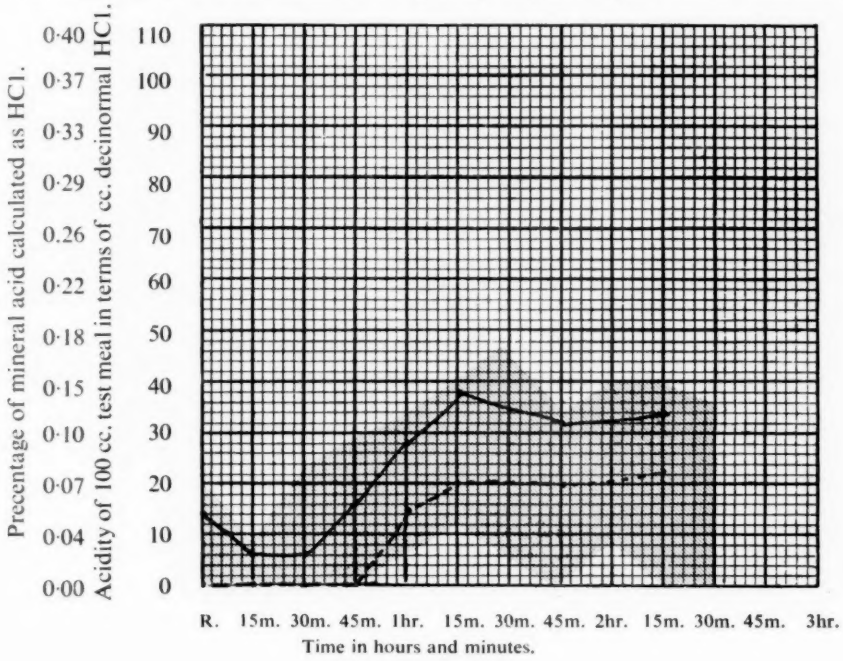

FIG. 4.—Case 3.

still present after 2¼ hours, bile and blood were absent throughout. Mucus occurred only in the resting juice.

BARIUM MEAL (fig. 5).—' Definite evidence of duodenal ulceration, recent,

FIG. 5.—Case 3.

with some mucosal oedema about half-way up the cap. There is a small degree of associated gastritis.'

After three weeks' medical treatment there was persistent scarring of the duodenal cap, suggesting fibrosis not oedema.

Case 4. P.C., aged seven years, admitted with abdominal pain and constipation. He had vomited once before admission, his tongue was furred, he was tender in the right iliac fossa, and a positive Rovsing sign was elicited. Per rectum he was extremely tender on the right side. His temperature was 99·6° F. and his pulse 96. He appeared flushed and was rather distressed. At laparotomy a normal appendix was removed and, therefore, further investigations were carried out. Urine and chest: nothing abnormal.

FRACTIONAL TEST MEAL (fig. 6).—There was no resting juice in the fractional

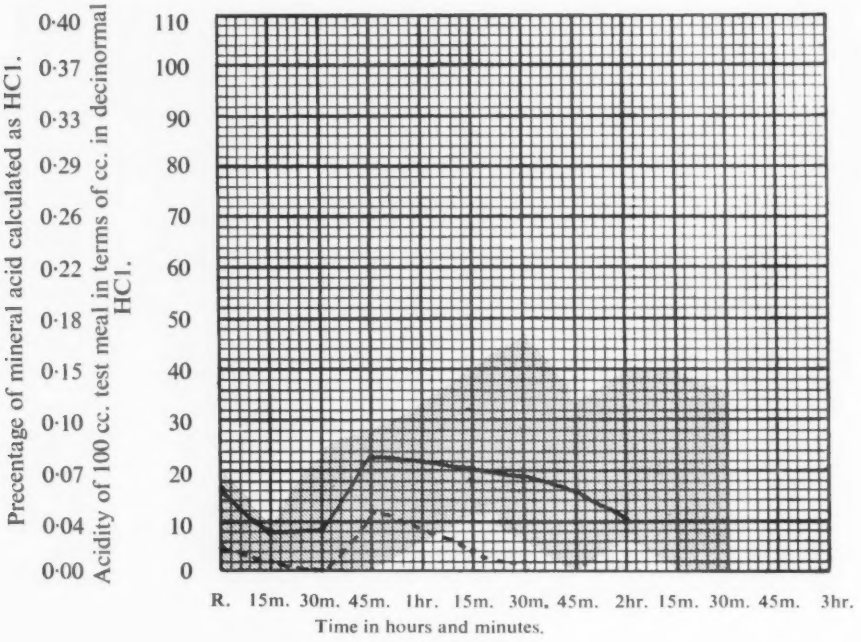

FIG. 6.—Case 4.

test meal. The total acidity remained low throughout, only rising to 23 after one hour and slowly dropping to 20 after one-and-a-half hours. The free HCl content never rose beyond 10. Microscopy revealed similar features to the cases previously described, namely squamous epithelial cells and a few pus cells. Bile and blood were absent.

BARIUM MEAL (fig. 7).—'The duodenal cap shows a persistent slight deformity caused by scarring from a small duodenal ulcer. No evidence of activity now or delay in emptying.' After three months of strict medical treatment, the appearances of the duodenal cap were those of cicatrization from a small ulcer on either the posterior or anterior wall, with no delay in emptying and no general deformity. There was a small excess of secretion in the stomach.

Discussion

It is obvious that no definite conclusions can be reached from so short a series of cases, and the main object in publishing them is to draw attention to the possibility of such a diagnosis in young children.

The first investigation of duodenal ulcers in children was carried out on a large scale by Theile (1919), who classified them in three groups:

Neonatal: Secondary to thrombosis, or associated with melaena neonatorum of unknown origin.

Infancy: Secondary to marasmus, tuberculosis, syphilis, scarlet fever, burns, uraemia, trauma and inflammations.

Childhood: Primary chronic round ulcer.

The first two groups contain a large number of cases, but little attention appears to have been directed to the third group occurring in childhood. In 1920 Moynihan stated that chronic peptic ulcer could often be traced back to the age of ten years and earlier. Proctor (1925) investigated the histories of

FIG. 7.—Case 4.

a thousand cases of duodenal ulcer and a thousand cases of gastric ulcer. He found that twenty-six cases of duodenal and sixteen of gastric ulcer gave a history which dated back to childhood. On the other hand, only three cases of duodenal ulcer in children were admitted to the Mayo clinic for treatment out of a total of ten thousand cases of peptic ulceration.

Hirsch (1935) reports after extensive statistical survey of 10,845 cases of peptic ulcer that 0·3 to 1·0 per cent. occurred in children, but most of these occurred in children of the youngest age group. Berglund (1928) reporting from a Swedish Children's Hospital concurred with this view, and stated that 1·4 per cent. of all post-mortem examinations during the first year of life reveal a duodenal ulcer. At a later age group Sturtevant and Shapiro (Conklin, 1941) reporting on 7,219 necropsies found that there were five cases of gastric ulcer in children.

In this country Hurst and Stewart (1929) in an analysis of two hundred cases of peptic ulceration found none in the first decade, but eight occurred in the second. In the United States, on the other hand, several more recent surveys have been made; Bloch, Bronstein and Serby (1932) reported four cases aged five, nine, eleven and thirteen years respectively. The first three were girls. Burdick (1940) reported ten cases in children. Moore (1941) in Canada had eight cases, and his conclusions will be mentioned later. In Italy, Toro (1937) described three cases and Bignami (1939) four cases, diagnosed radiologically. In Russia, Gerasimov (1939) reported a case of perforation of a duodenal ulcer in a child aged three-and-a-half.

In Great Britain, Smyth, Crymble and Allen (1934) mentioned a case of duodenal ulcer occurring in a girl of ten. Miller and Gage (1930) found a cicatrizing chronic duodenal ulcer in a girl of seven. The sex incidence of ulcers in children was investigated by Saltzstein, Farbman and Sandweiss (1940), who found 105 cases in the literature up to 1940, most of them in infants. From their records they came to the conclusion, that whereas peptic ulcer is by far more prevalent in adult men than women, its occurrence among children was spread equally over both sexes.

As far as clinical features are concerned Kennedy (1933) stated that in children below the age of ten the familiar syndrome of an uncomplicated ulcer is absent. Two out of his six cases had appendicectomies performed. He thought that it was neither necessary nor desirable to determine the gastric acidity in children. John (1938) described a rather unusual case, in which a child of six was admitted with a temperature of 103° F. and a pulse of 120, a coated tongue, with tenderness but no rigidity in the right iliac fossa. Appendicectomy was performed and two stercoliths were found in the appendix. A few days later the child died from a haematemesis due to a large ulcer crater in the first part of the duodenum. Moore (1941) has seen eight cases of duodenal ulcer in children, three of these being admitted as cases of acute appendicitis. Six of his cases had abdominal tenderness and nearly all of them had either vomited or felt sick before admission. He also mentions that he found that gastric analyses were inconclusive. His cases were treated medically and found to respond satisfactorily.

There appears to have been a great increase in the number of cases diagnosed since Proctor of the Mayo Clinic stated in 1925 that only nineteen cases of primary duodenal ulcer in children had been described in the literature.

Conclusions

As far as the new cases here described are concerned, the following facts seem worthy of mention.

History.—There was no typical prolonged history comparable with the adult symptoms of pain occurring after food. One of the cases, however (the girl of thirteen), is still complaining of occasional pain, which has now, four months after the start of medical treatment, begun to bear some relation to meals.

In all cases there was a history of only a few hours' pain before admission. Nausea or vomiting were present in three cases, but had not occurred more than once in any one case.

Physical signs.—(1) Temperature and pulse were raised in all cases. The temperature varied from 99·0° to 102·2° F. The pulse rate appeared to be increased approximately in proportion to the temperature.

(2) Tenderness was localized in three cases to the right iliac fossa only, and in one case occurred in both iliac fossae.

(3) Rigidity was present in two cases ; this was not confined to the right side only, but extended to the left side as well.

(4) Tenderness per rectum was found in all cases. But this cannot be conclusive, as it is difficult to be certain whether the examination is not merely causing discomfort.

Special tests.—(1) A leucocyte count of 17,000 per c.mm. occurred in one

case, but appears to be quite irrelevant to the ulcer condition. The leucocyte counts in the other cases were quite inconclusive.

(2) Gastric analyses.—Out of three cases in which these were performed, one had a normal curve; one only had a raised acidity (the girl), and even here the readings are hardly above the normal limit; the third had a very low acidity curve. In the main we agree with Moore and Kennedy, who both state that gastric analyses are inconclusive.

(3) Barium meal.—All the ulcers occurred in the first part of the duodenum and varied from mere mucosal swelling to well formed craters surrounded by mucosal oedema.

After medical treatment the deformity still persisted, having become permanent owing to fibrosis and thickening in two of our cases.

Thanks are due to Dr. Stewart Russell Reynolds for his co-operation in carrying out the barium meal examinations and allowing the reproduction of his reports on the x-ray pictures.

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NOTICE

Restrictions upon the consumption of paper imposed by the paper control as this issue of the ARCHIVES OF DISEASE IN CHILDHOOD was about to go to press, has necessitated a reduction in the number of pages published and the consequent holding over of a number of papers already in type.

Although future arrangements are uncertain it is hoped to continue regular publication.

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